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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP). SETOI, Hiroyuki [JP/JP]; 4-13-1, Namiki, Tsukuba-shi, Ibaraki 305 (JP). KAYAKIRI, Hiroshi [JP/JP]; 2-31-15, Umezono, Tsukuba-shi, Ibaraki 305 (JP). SATOH, Shigeki [JP/JP]; 3-25-4-304, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). INOUE, Takayuki [JP/JP]; 2-11-18-202, Takezono, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Yuki [JP/JP]; 1-602-208, Azuma, Tsukuba-shi, Ibaraki 305 (JP). KURODA, Akio [JP/JP]; 2-221, Gokasho, Hirookadani, Uji-shi, Kyoto 611 (JP). TANAKA, Hirokazu [JP/JP]; 1-4-8, Ottominami, Tsuchiura-shi, Ibaraki 300 (JP).

(74) Agent: YOSHIKAWA, Toshio; New Wakasugi Bldg. 8F, 1-21-14, Higashinodacho, Miyakojima-ku, Osaka-shi, Osaka 534 (JP).

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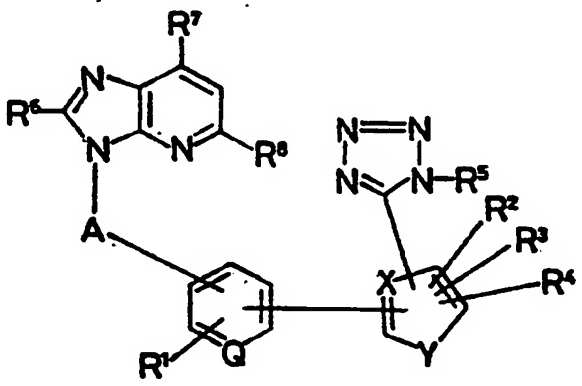
(54) Title: IMIDAZOPYRIDINE DERIVATIVES AS ANGIOTENSIN II ANTAGONISTS



(I)

(57) Abstract

The object compound of the formula (I): wherein R^1 is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, amino r acylamino, R^2, R^3 and R^4 are each hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkylthio, mono or di or trihalo (lower)alkyl, oxo (lower)alkyl, hydroxy (lower)alkyl or optionally esterified carboxy; or R^2 and R^3 are linked together to form 1, 3-butadienylene, R^5 is hydrogen or imino-protective group, R^6 is lower alkyl, R^7 is lower alkyl, R^8 is optionally esterified or amidated carboxy, halogen, cyano, hydroxy (lower)alkyl, or lower alkoxy which may have halogen, A is lower alkylene, Q is CH or N, X is N or CH and Y is NH, O or S, and pharmaceutically acceptable salts thereof which are useful as a medicament.

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DESCRIPTION

Imidazopyridine derivatives as Angiotensin II antagonists

TECHNICAL FIELD

The present invention relates to novel heterocyclic derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel imidazole derivatives and a pharmaceutically acceptable salt thereof which have pharmaceutically activities such as angiotensin II antagonism and the like, to process for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide novel imidazole derivatives and a pharmaceutically acceptable salt thereof, which are useful as a potent and selective antagonist of angiotensin II receptor.

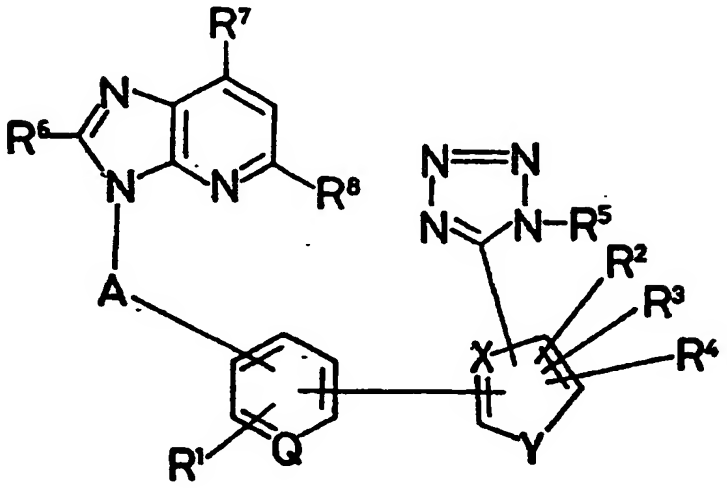
Another object of the present invention is to provide process for preparation of said imidazole derivatives or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said imidazole derivatives or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said imidazole derivatives or a pharmaceutically acceptable salt thereof as a medicament such as angiotensin II antagonist useful for treating or preventing angiotensin II mediated diseases, for example, hypertension (e.g. essential hypertension, renal hypertension, etc.), heart failure, and the like in human being or animals.

DISCLOSURE OF INVENTION

The imidazole derivatives of the present invention are novel and can be represented by the formula (I):



(I)

wherein R^1 is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, amino or acylamino,

R^2, R^3 and R^4 are each hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkylthio, mono or di or trihalo (lower) alkyl, oxo (lower) alkyl, hydroxy (lower) alkyl or optionally esterified carboxy ; or

R^2 and R^3 are linked together to form 1,3 — butadienylene,

R^5 is hydrogen or imino — protective group,

R^6 is lower alkyl,

R^7 is lower alkyl,

R^8 is optionally esterified or amidated carboxy, halogen, cyano, hydroxy (lower) alkyl, or lower alkoxy which may have halogen,

A is lower alkylene,

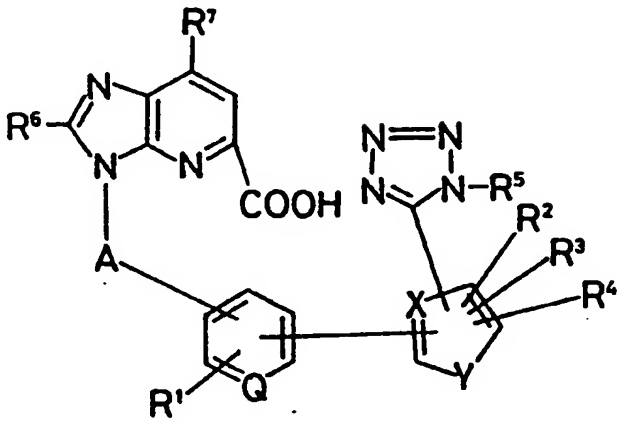
Q is CH or N,

X is N or CH and

Y is NH, O or S.

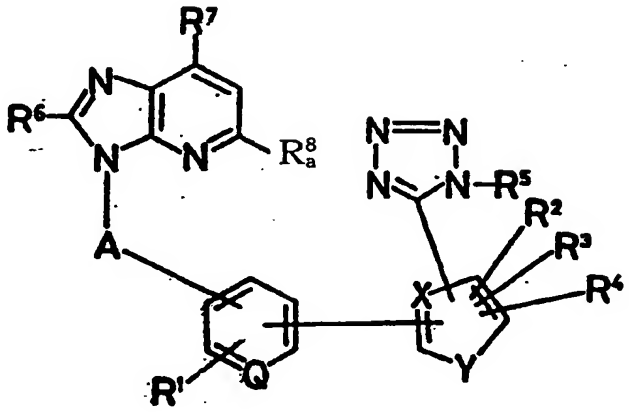
According to the present invention, the object compound (I) can be prepared by the following processes.

Process 6



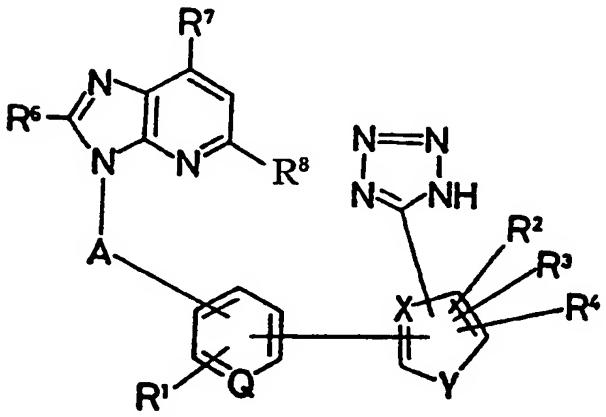
Esterification

(I-b)
or its reactive derivative at the carboxy group
or a salt thereof



(I-a)
or a salt thereof

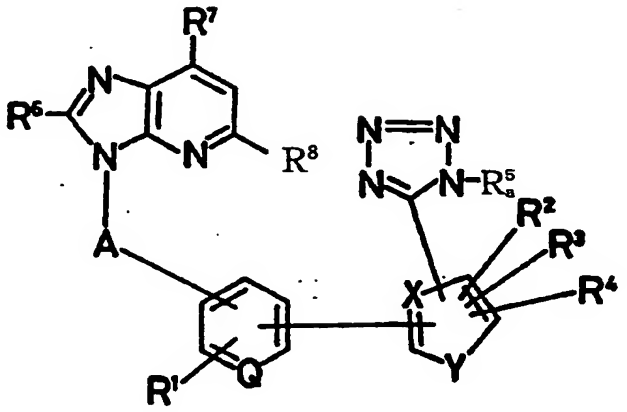
Process 7



Introduction of the imino-protective group

(I-d)

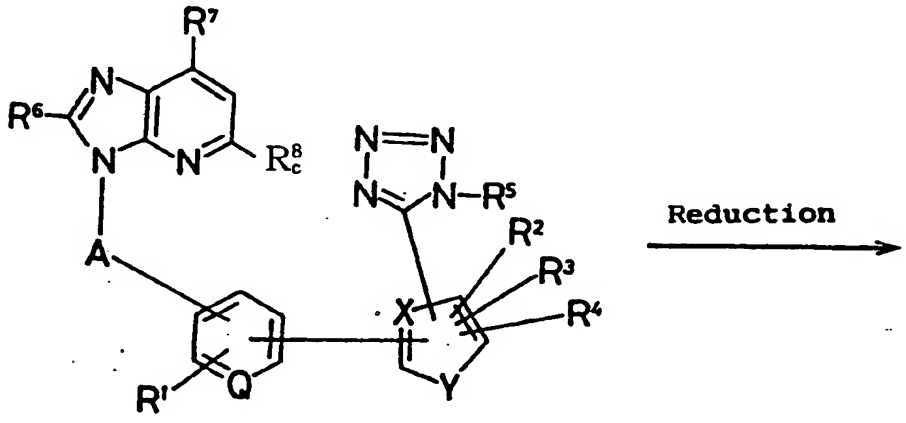
or a salt thereof



(I-c)

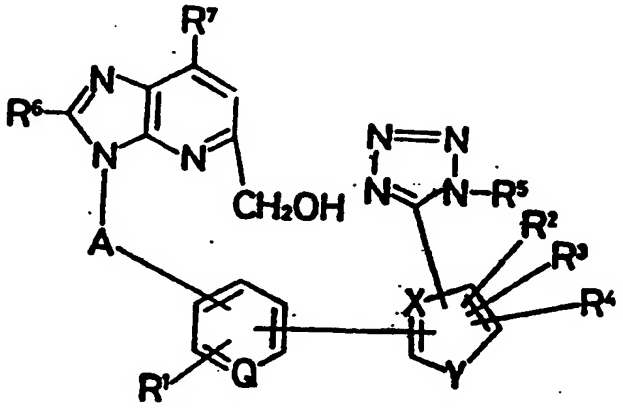
or a salt thereof

Process 8



(I-f)

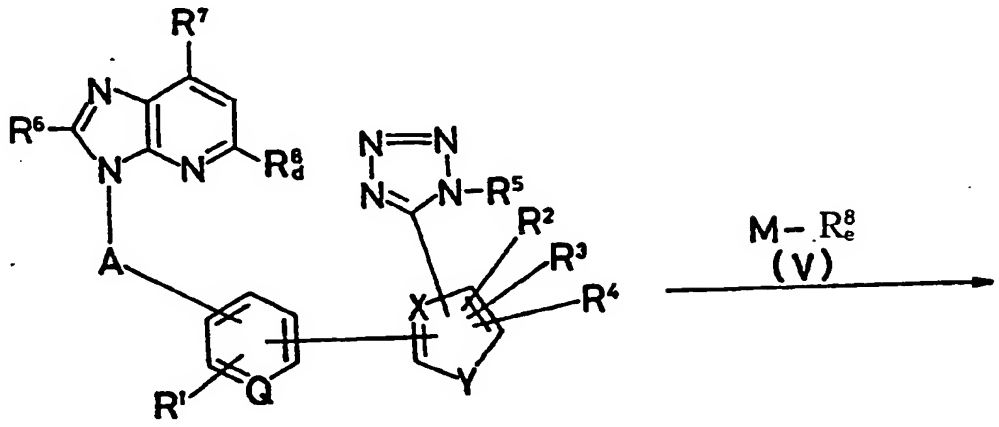
or a salt thereof



(I-g)

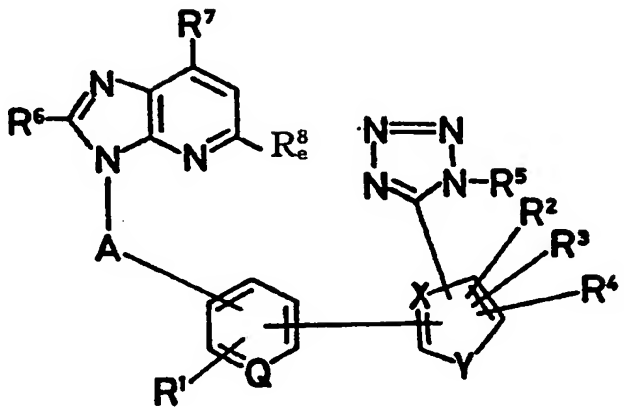
or a salt thereof

Process 9



(I-h)

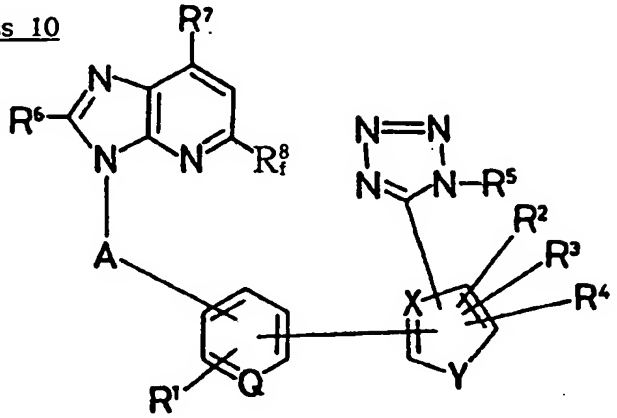
or a salt thereof



(I-i)

or a salt thereof

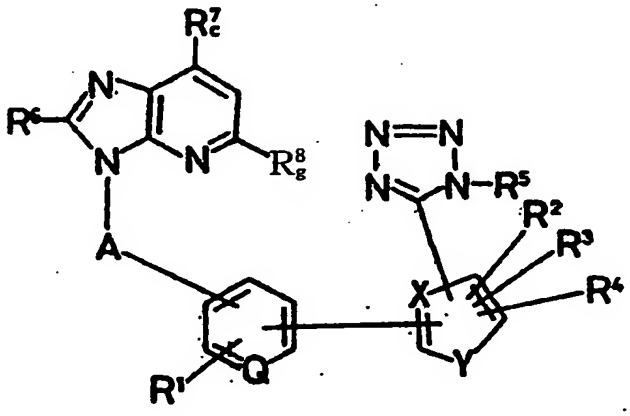
Process 10



Elimination of the ester moiety

(I-j)

or a salt thereof



(I-k)

or a salt thereof

Wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, Q, X and Y are each as defined above,

R_c^5 is imino-protective group,

R_c^8 is esterified carboxy,

R_d^8 is amidated carboxy,

R_e^8 is optionally esterified carboxy,

R_d^5 is halogen,

R_e^8 is lower alkoxy which may have halogen,

R_f^8 is amidated carboxy having esterified carboxy,

Suitable salts of the compound (I) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkali earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.);and the like, and the preferable example thereof is an acid addition salt.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl group in the term "lower alkylthio" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, preferably one having 1 to 5 carbon atoms, and the like.

Suitable "lower alkenyl" may include vinyl, 1-propenyl, allyl, 1-butenyl, 2-butenyl, 2-pentenyl, and the like, preferably one having 2 to 4 carbon atoms, in which the most preferred one is vinyl.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, dimethylethylene, hexamethylene, and the like, in which the preferred one is methylene.

Suitable "halogen" means fluoro, chloro, bromo and iodo.

Suitable "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which the preferable one is C_1-C_4 alkoxy.

Suitable acyl group in the term "acylamino" may include carbamoyl, thiocarbamoyl, sulfamoyl, aliphatic acyl, aromatic acyl, heterocyclic acyl, in which the preferable one is aliphatic acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, hexanoyl, etc.), lower alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, etc) and the like.

Suitable "mono or di or trihalo(lower)alkyl" may include chloromethyl, fluoromethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trifluoromethylpropyl, and the like.

Suitable "lower alkoxy which may have halogen" may include lower alkoxy as mentiond above mono-(or di- or tri-)halo(lower)alkoxy (e.g. chloromethoxy, fluoromethoxy, difluoromethoxy, dichloromethoxy, trifluoroethoxy, trifluoropropoxy and the like.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, hydroxyethyl, and the like.

Suitable "oxo(lower)alkyl" may include formyl, formylmethyl, formylethyl, and the like.

Suitable "ester moiety" in "esterified carboxy group" may include pharmaceutically acceptable, easily removable one such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), lower alkoxy (lower)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.), lower alkylthio(lower)-alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.), carboxy-substituted-lower alkyl ester (e.g. carboxymethyl ester, 2-

carboxyethyl ester, 3-carboxypropyl ester, etc.), protected carboxy-substituted-lower alkyl ester such as lower alkoxycarbonyl-substituted-lower alkyl ester (e.g. methoxycarbonylmethyl ester, tert-butoxycarbonylmethyl ester, 2-tert-butoxycarbonyl-ethyl ester, 3-tert-butoxycarbonylpropyl ester, etc.), protected carboxy-substituted-lower alkenyl ester such as lower alkoxycarbonyl-substituted-lower alkenyl ester (e.g. 2-isobutoxycarbonyl-2-pentenyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower) alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.], higher alkanoyloxy(lower)-alkyl ester [e.g. heptanoyloxymethyl ester, octanoyloxymethyl ester, nonanoyloxymethyl ester, decanoyloxymethyl ester, undecanoyloxymethyl ester, lauroyloxymethyl ester, tridecanoyloxymethyl ester, myristoyloxymethyl ester, pentadecanoyloxymethyl ester, palmitoyloxymethyl ester, heptadecanoyloxymethyl ester, stearoyloxymethyl ester, nonadecanoyloxymethyl ester, eicosanoyloxymethyl ester, 1(or 2)-heptanoyloxyethyl ester, 1(or 2)-octanoyloxyethyl ester, 1(or 2)-nonanoyloxyethyl ester, 1(or 2)-decanoyloxyethyl ester, 1(or 2)-undecanoyloxyethyl ester, 1(or 2)-lauroyloxyethyl ester, 1(or 2)-tridecanoyloxyethyl ester, 1(or 2)-myristoyloxyethyl ester, 1(or 2)-pentadecanoyloxyethyl ester, 1(or 2)-palmitoyloxyethyl ester, 1(or 2)-heptadecanyloxyethyl ester, 1(or 2)-stearoyloxyethyl ester, 1(or 2)-nonadecanoyl-oxyethyl ester, 1(or 2)-eicosanoyloxyethyl ester, etc.], cycloalkylcarbonyloxy(lower)alkyl ester [e.g. cyclohexylcarbonyloxymethyl ester, 1(or 2) -cyclopentylcarbonyloxyethyl ester, 1 (or 2) -cyclohexylcarbonyloxyethyl ester, etc,], aroyloxy (lower)

alkyl ester such as benzoyloxy(lower)alkyl ester [e.g. 1 (or 2) -benzoyloxyethyl ester, etc,] heterocycliccarbonyloxy(lower)alkyl ester such as lower alkylpiperidylcarbonyloxy(lower)alkyl ester [e.g. 1 (or 2) -(1-methylpiperidyl)carbonyloxyethyl, etc.], lower alkoxycarbonyloxy(lower)alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, isopropoxycarbonyl-oxymethyl ester, tert-butoxycarbonyloxymethyl ester, 1(or 2)-methoxycarbonyloxyethyl ester, 1(or 2)-ethoxycarbonyloxyethyl ester, 1(or 2)-propoxycarbonyloxyethyl ester, 1(or 2)-isopropoxycarbonyloxyethyl ester, 1(or 2)-butoxycarbonyloxyethyl ester, 1(or 2)-isobutoxycarbonyloxyethyl ester, 1(or 2)-tert-butoxycarbonyloxyethyl ester, 1(or 2)-hexyloxycarbonyloxy-ethyl ester, 1(or 2 or 3)-methoxycarbonyloxypropyl ester, 1(or 2 or 3)-ethoxycarbonyloxypropyl ester, 1(or 2 or 3)-isopropoxycarbonyloxypropyl ester, 1(or 2 or 3 or 4)-ethoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4)-butoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4 or 5)-pentyloxycarbonyloxypentyl ester, 1(or 2 or 3 or 4 or 5)-neopentyloxycarbonyloxypentyl ester, 1(or 2 or 3 or 4 or 5 or 6)-ethoxycarbonyloxyhexyl ester, etc.], cycloalkyloxycarbonyloxy(lower)alkyl ester [e.g. cyclohexyloxycarbonyloxymethyl ester, 1(or 2)-cyclopentyloxycarbonyloxyethyl ester, 1(or 2)-cyclohexyloxycarbonyloxyethyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, (5-tert-butyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], (5-aryl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylmethyl ester, etc.), ar(lower)alkyl ester which may have one or more substituent(s) such as mono-(or di or tri)phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)-

methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, 1(or 2)-phthalid-3-ylideneethyl ester, etc.), and the like.

Suitable "imino-protective group" may include conventional one, and the preferable example thereof is ar(lower)alkyl such as mono-(or di- or tri-) phenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), acyl such as lower alkoxycarbonyl (e.g. tert-butoxycarbonyl, etc.), lower alkanesulfonyl (e.g. mesyl, etc.), arenesulfonyl (e.g. tosyl, etc.), and the like, in which the most preferred one is trityl.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.) and the like.

Suitable "amidated carboxy" may carbamoyl which may have suitable substituent(s) and may include carbamoyl, mono or di (lower) alkylcarbamoyl (e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, butylcarbamoyl, t-butylcarbamoyl, etc.), lower alkylarylcarbamoyl (e.g. isobutylphenylcarbamoyl, etc.), hydroxy(lower)alkylcarbamoyl(e.g. hydroxymethylcarbamoyl, etc.), N-hydroxy-N-(lower)alkylcarbamoyl(e.g. N-hydroxy-N-methylcarbamoyl, etc.), acylcarbamoyl such as lower alkylsulfonylcarbamoyl (e.g. mesylcarbamoyl, etc.), carbamoyl having optionally esterified carboxy such as phenyl(lower)alkylcarbamoyl, in which lower alkyl moiety is substituted by optionally esterified carboxy, for example, 1-carboxyphenethylcarbamoyl, 1-(lower alkoxycarbonyl) phenethylcarbamoyl (e.g. 1-(lower alkoxycarbonyl)phenethylcarbamoyl (e.g. 1-(ethoxycarbonyl)phenethylcarbamoyl, etc.) and the like.

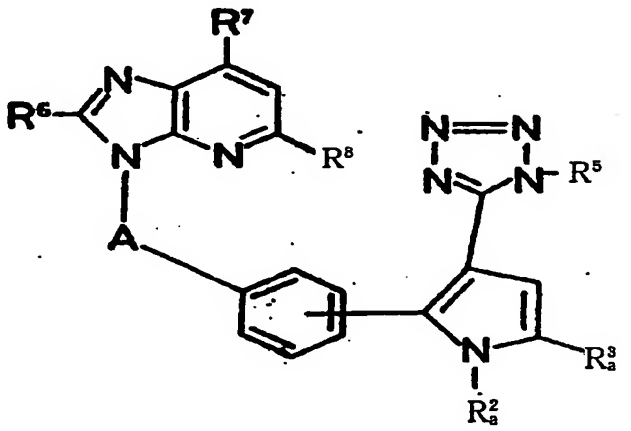
Suitable "amidated carboxy having carboxy" may include phenyl(lower) alkylcarbamoyl, in which lower alkyl moiety is substituted by carboxy, 1-carboxyphenethylcarbamoyl, etc.), and the like.

Suitable "amidated carboxy having esterified carboxy" may include phenyl(lower)alkylcarbamoyl, in which lower alkyl moiety is substituted by

esterified carboxy, such as 1-(loweralkoxycarbonyl)phenethylcarbamoyl (e.g. 1-(ethoxycarbonyl)phenethylcarbamoyl, etc.) and the like.

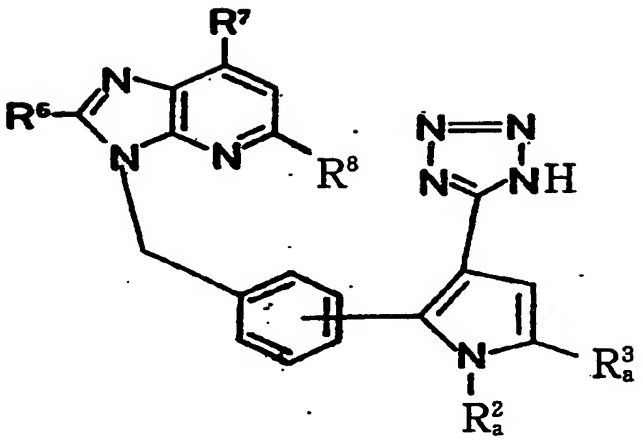
Suitable "alkali metal" may include sodium, potassium, cesium, and the like.

The preferred embodiment of the heterocyclic derivatives (I) of the present invention can be represented by the following chemical formula:



(I — 1)

Particularly, the preferred compound (I) of the present invention is represented by the following chemical formula :



(I — 2)

wherein R^6, R^7, R_a^2 and R_a^3 are each lower alkyl, and

R^8 is carboxy, lower alkoxycarbonyl, carbamoyl, mono — or di (lower) alkylcarbamoyl, N — hydroxy — N — (lower) alkylcarbamoyl, lower alkylsulfonylcarbamoyl, 1 — carboxyphenethylcarbamoyl, 1 — (lower alkoxycarbonyl) phenethylcarbamoyl, halogen, cyano, hydroxy (lower) alkyl or lower alkoxy which may have halogen.

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1 :

The object compound (I) or a salt thereof can be prepared by subjecting the compound (II) to the formation reaction of a tetrazole group.

The agent to be used in the present reaction may include conventional ones which is capable of converting a cyano group to a tetrazolyl group such as metal azide, for example, alkali metal azide(e.g., potassium azide, sodium azide etc.), tri(lower)alkyltin azide(e.g. trimethyltin azide, etc.), triaryltin azide (e.g. triphenyltin azide, etc.), or the like.

The present reaction is usually carried out in the presence of a base such as tri(lower)alkylamine(e.g. triethylamine, etc.), and the like, or 1,3-dimethyl-2-imidazolidinone, and the like.

The present reaction is usually carried out in a solvent such as xylene, dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, dimethylformamide or any other

solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming or heating, preferably under heating.

Process 2 :

The object compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to the elimination reaction of the ester moiety.

Suitable method for this reaction may include conventional one such as hydrolysis, and the like.

The hydrolysis is to be referred to those as explained in process 4.

Process 3 :

The object compound (I) or a salt thereof can be prepared by reacting the compound (III) or a salt thereof with the compound (IV) or a salt thereof.

The present reaction is usually carried out in the presence of a base such as alkyl lithium (e.g. n-butyl lithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), di(lower)alkylamine (e.g. diisopropylamine, etc.), tri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, tetrahydrofuran, or any other solvent which does not adversely affect the reaction. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 4 :

The object compound (I-d) or a salt thereof can be prepared by

subjecting the compound (I-c) or a salt thereof to removal reaction of the imino-protective group.

Suitable method for this removal may include conventional one which is capable of removing an imino-protective group on a tetrazolyl group such as hydrolysis, reduction, or the like. The hydrolysis is preferably carried out in the presence of the base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e. g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e. g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate, (e. g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e. g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e. g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e. g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e. g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e. g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e. g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4,3,0]non-5-one, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]-undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e. g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e. g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 5:

The object compound (I-e) or a salt thereof can be prepared by

subjecting the compound (I-b) or its reactive derivative at the carboxy group or a salt thereof to amidation reaction.

Suitable salt of the compound (I-e) can be referred to the salt exemplified for the compound (I).

The amidating agent to be used in the present amidation reaction may include amine which may have suitable substituent(s).

Suitable reactive derivative at the carboxy group of the compound (I-b) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulforous acid, thiosulfuric acid, sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresylthioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.), and the like.

When the compound (I-b) is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide, 1,1'-carbonyldi-imidazole, thionyl chloride, oxalyl chloride, lower lower alkoxycarbonyl halide [e.g. ethyl

chloroformate, isobutyl chloroformate, etc.], 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction in the presence of a condensing agent is usually carried out in an anhydrous, but not critical conditions.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), tri (lower) alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

In case that the base or the condensing agent to be used is in liquid, it can be used also as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out under heating or under warming, preferably under heating.

Process 6

The compound (I-a) or a salt thereof can be prepared by subjecting the compound (I-b) or its reactive derivative at the carboxy thereof, or a salt thereof to esterification.

The reaction can be carried out by a conventional esterification.

Suitable reactive derivative at the carboxy group of the compound (I-b) may be the same as those exemplified in Process 5.

Suitable esterifying agent used in this reaction may include alcohol or its conventional reactive derivative such as halide, (e.g. cyclohexyl 1-iodomethyl carbonate, cycohexyl 1-iodoethyl carbonate, etc.) sulfonate, and the like. Further, it may include di (lower) alkylsulfate (e.g.

dimethylsulfate, etc.), diazo (lower) alkanes (e.g. diazomethane, etc.), 3-lower alkyltriazenes (e.g. 3-methyl-1-tolyltriazene, etc.), and the like.

This reaction is usually carried out in a conventional solvent such as alcohols(e.g. methanol, ethanol, etc.), dioxane, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 7

The object compound (I-c) can be prepared by subjecting the compound (I-d) to introduction reaction of the imino protective group.

The introduction reaction of the imino protective group in this step can be carried out by reacting the compound (I-d) with a suitable agent for introducing the imino protective group.

Suitable examples of said agent may be ar(lower)alkyl halide which may have aforesaid lower alkoxy such as phenyl(lower)alkyl halide which may have lower alkoxy (e.g. benzyl iodide, 3-methoxybenzyl iodide, benzyl bromide, 4-methoxybenzyl bromide, phenethyl chloride, etc.), diphenyl(lower) alkyl halide (e.g. benzhydryl chloride, etc.), triphenyl(lower)alkyl halide (e.g. tritylchloride, tritylbromide, etc.) or the like.

This introduction reaction may be carried out in a suitable solvent such as chloroform, acetonitrile, acetone, nitrobenzene, N,N-dimethylformamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and usually carried out at room temperature, under warming or under heating.

Process 8

The compound (I-g) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to reduction.

This reduction may include, for example, reduction with an alkali metal borohydride (e.g. sodium borohydride, lithium aluminum hydride, and th

like.

This reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, etc.), dioxane, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

Process 9

The object compound (I-i) or a salt thereof can be prepared by reacting the compound (I-h) or a salt thereof with the compound (V) or a salt thereof.

This present reaction is usually carried out in a conventional solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating, preferably under heating.

Process 10

The object compound (I-k) or a salt thereof can be prepared by subjecting the compound (I-j) or a salt thereof to elimination reaction of the ester moiety.

Sutable method for this reaction may include conventional one such as hydrolysis, and the like.

The hydrolysis is to be referred to those as explained in process 4.

The starting compounds (II), (III) and (IV) are new and can be prepared by the methods of Preparations mentioned below or a similar manner thereto or a conventional manner.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, estraction precipitation, fractional crystallization, recrystallization, chromtography, and the like.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The object compound (I) of the present invention exhibits angiotensin antagonism such as vasodilating activity and is useful as an angiotensin II antagonist and effective to various angiotensin II mediated diseases such as hypertension (e.g. essential hypertension, renal hypertension, etc.), heart failure, and the like.

Further, it is expected that the object compounds of the present invention are useful as therapeutical and/or preventive agents for cardiopathy (e.g. angina pectoris, arrhythmia, myocardial infarction, etc.), hyperaldosteronism, cerebral vascular diseases, senile dementia, ophthalmic diseases (e.g. glaucoma, etc.), and the like; and diagnostic agents to test the renin angiotensin system.

For therapeutic or preventive administration, the object compound(I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral, external and inhalant administration. The pharmaceutical preparation may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary form and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound (I) to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Examples are given for the purpose of

illustrating the present invention.

Preparation 1

To 1,1-Diethoxybutane (591.6g) was added calcium carbonate (243g) keeping at -16 ~ -18 ℃.
To the mixture was added dropwise bromine (208.8ml) during a period of 3 hours at -12℃ and the mixutre was stirred at 5℃ for 2 hours. The reaction mixture was diluted with diethyl ether(1ℓ)and the insoluble product was filtered off. The aqueous layer was separated and was added sodium bicarbonate powder (300g).
To the mixture was added dropwise the ether phase with stirring and washed with saturated sodium bicarbonate (1ℓ × 2), water(1ℓ) and saturated sodium chloride (500ml) and dried over potassium carbonate. The solvent was evaporated in vacuo to give the crude product. To the crude product was added potassium carbonate (20g) and the mixture was kept at 5 ℃.
The mixture was distilled under reduced pressure to give 2-bromo-1,1-diethoxybutane (450g) as colorless oil.
bp : 45-55℃

NMR ($CDCl_3$, δ) : 1.05(3H,t,J=7.5Hz),
1.24(6H,tx2,J=7.5Hz), 1.53-1.90(2H,m),
1.91-2.20(2H,m), 3.48-3.83(4H,m),
3.93(1H,ddd,J=4,6 and 9Hz), 4.54(1H,d,J=6Hz)

Preparation 2

Potassium carbonate neat (322g) was added to 2-bromo-1,1-diethoxybutane (450g) and stirred.
To the mixture was added benzyl amine (438ml)and the mixutre was allowed to heat to 130℃ for 16.5 hours with vigorous stirring.
After cooled, to the mixture was added in sodium hydroxide (1ℓ) with stirring.
The separated oil was extracted with phenol (2ℓ). The organic layer was washed with water (1ℓ) and saturated sodium chloride (0.5ℓ), dried over magnesium sulfate, and evaporated. The residue distilled to give 1,1-diethoxy-2-benzylaminobutane (383.86g) as colorless oil.
bp : 95-106 ℃
NMR ($CDCl_3$, δ) : 0.94(3H,t,J=7.5Hz),
1.20 (3H× 2,t,J=7.5Hz), 1.37-1.80(2H,m),
1.66(1H,br,s), 2.63(1H,q,J=5Hz),
3.40-3.90(6H,m), 4.38(1H,d,J=6Hz),
7.14-7.41(5H,m).

Preparation 3

A mixture of 1,1-diethoxy-2-benzylaminobutane (40.0g),10% palladium on carbon (2.0g), and ethanol (150ml) was allowed to heat to 56 ℃ with vigorous stirring under hydrogen atmosphere (3~4atm) and was stood overnight and was filtered through celite and the filtrate was evaporated in vacuo. The residue was distilled in vacuo to give 2-amino-1,1-diethoxybutane (14.56g) as colorless oil.
bp : 40-43℃

Preparation 4

A mixture of
4-(methoxycarbonyl)benzoylacetonitrile (16.4g) and

1,1-diethoxy-2-aminobutane (13.00g) in toluene (160ml) was refluxed for 8 hours.
After being cooled, was evaporated in toluene. To the residue was added trifluoroacetic acid (65ml) under ice-cooling, and the mixture was stirred at 0 ℃ for 30 minutes. Cold diethyl ether (70ml) was added to the reaction mixture. The precipitate was collected by filtration and washed successively with cold diethyl ether (100ml) and cold ethyl acetate (50ml).
After drying in air, the residue was purified by preparative thin layer chromatography to give crude product of 5-ethyl-2-(4-methoxycarbonylphenyl)pyrrole-3-carbonitrile(10.96g) which was used for the next reaction without further purification.

Preparation 5

To a suspension of 5-ethyl-2-(4-methoxycarbonylphenyl)pyrrole-3-carbonitrile) (5.0g) in dimethylformamide (50ml) was added sodium hydride (1.03g) portionwise at room temperature. To the mixture was added dropwise ethyl iodide (7.9ml) and the mixture was stirred for 4 hours. The resulting mixture was quenched with saturated ammonium chloride, extract with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and evaparated in vacuo. The residue was purified by flash column chromatography (elution by ethyl acetate/n-hexane=1:7 → 1:5) to yield 1,5-diethyl-2-(4-methoxycarbonylphenyl)pyrrole-3-carbonitrile (4.20g) as colorless viscous oil.

NMR ($CDCl_3$, δ) : 1.17(3H,t,J=7.5Hz),
1.33(3H,t,J=7.5Hz), 2.64(2H,q,J=7.5Hz),
3.90(2H,q,J=7.5Hz), 3.95(3H,s), 6.29(1H,s),
7.51(2H,d,J=9Hz), 8.14(2H,d,J=9Hz)

Preparation 6

To a solution of 1,5-diethyl-2-(4-methoxycarbonylphenyl)pyrrole-3-carbonitrile (4.10g) in tetrahydrofuran (40ml) was added dropwise lithium borohydride (16.1ml) at ambient temperature and the mixture was refluxed for 5 hours. The mixture was quenched with saturated aqueous ammonium chloride solution under ice-cooling and water was added to the mixture and extracted with ethyl acetate.
The extract was washed with saturated sodium bicarbonate, water and saturated sodium chloride, dried, and concentrated in vacuo to give 1,5-diethyl-2-(4-hydroxymethylphenyl)pyrrole-3-carbonitrile (3.74g) as yellow oil.

NMR ($CDCl_3$, δ) : 1.16(3H,t,J=7.5Hz), 1.30(3H,t,J=7.5Hz), 1.88(1H,br,s), 2.62(2H,q,J=7.5Hz), 3.89(2H,q,J=7.5Hz), 4.75(2H,s), 6.23(1H,s), 7.41(2H,d,J=9Hz), 7.49(2H,d,J=9Hz)

Preparation 7

To a solutaion of 1,5-diethyl-2-(4-hydroxymethylphenyl)pyrrole-3-carbonitrile (1.75g) in dichlomethane (35ml) was added triethylamine (1.80ml). To the mixture was added dropwise methanesulfonyl chloride (0.53ml) under ice methanol-cooling and the mixture was stirred at the same temperature for one hour. The reaction mixture was diluted with dichloromethane, washed with water, saturated sodium bicarbonate and saturated sodium chloride, dried over magnesium sulfate and eveporated in vacuo with toluene (twice) to give 1,5-diethyl-2-(4-methanesulfonyloxymethylphenyl)pyrrole-3-carbonitrile (2.73g) as yellow viscous oil.

NMR ($CDCl_3$, δ) : 1.17(3H,t,J=7.5Hz),
1.33(3H,t,J=7.5Hz), 2.63(2H,q,J=7.5Hz),
3.01(3H,s), 3.89(2H,q,J=7.5Hz), 5.28(2H,s),
6.25(1H,s), 7.48(2H,d,J=9Hz), 7.55(2H,d,J=9Hz)

Preparation 8

To a suspension of 5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridine (1.47g) in dimethylformamide (10ml) was added sodium hydride (60%:310mg) portionwise at room temperature. The mixture was stirred at the same temperature for 30 minutes. To the mixture was added a solution of 1,5-diethyl-2-(4-methanesulfonyloxymethylphenyl)pyrrole-3-carbonitrile (1.47g) in dimethylformamide (15ml). The mixture was stirred at ambient temperature for 40 minutes. The resulting mixture was quenched with saturated ammonium chloride, diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and evaparated in vacuo. The residue was purified by flash column chromatography (elution by ethyl acetate/n-hexane=1:4→ 1:1 → 2:1) and subsequent (1.662g) crystallization from diisopropyl ether to give 3-[4-(3-cyano-1,5-diethylpyrrol-2-yl)benzyl]-5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridine as colorless prism.
mp : 116-118℃
NMR ($CDCl_3$, δ) : 0.98(3H,t,J=7.5Hz),
1.12(3H,t,J=7.5Hz), 1.30(3H,t,J=7.5Hz),
1.75(2H,m), 2.49-2.66(2H,m), 2.60(3H,s),
2.64(3H,s), 2.67(2H,d,J=8Hz),
3.82(2H,q,J=7.5Hz), 5.50(2H,s), 6.21(1H,s),
6.90(1H,s), 7.20(2H,d,J=9Hz), 7.32(2H,d,J=9Hz).

Preparation 9

To a solution of 5-ethyl-2-(4-methoxycarbonylphenyl)pyrrole-3-carbonitrile

(5.0g) in dimethylformamide(50ml) was added sodium hydride (1.03g : 60% oil dispension) by portions and the stirring was continued for half an hour at the same temperature. Methyl iodide (6.13ml) was added dropwise to the mixture, and was stirred for 6 hours. The reaction mixture was quenched with ammonium chloride and diethyl ether was added. The organic layer was separated and washed successively with water and saturated sodium chloride, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel eluted with a mixture of n-hexane and ethyl acetate (7:1 to 3:1, V/V) to give a solid product. This product was washed with diisopropyl to give 5-ethyl-2-(4-methoxycarbonylphenyl)-1-methyl-pyrrole-3-carbonitrile (3.5g) as pale yellow solid.

mp : 131-132℃

NMR ($CDCl_3$, δ) : 1.30(3H,t,J=7.5Hz), 2.60(3H,q,J=7.5Hz), 3.50(3H,s), 3.95(3H,s), 6.26(1H,s), 7.52(2H,d,J=9Hz), 8.14(2H,d,J=9Hz)

Preparation 10

5-Ethyl-2-(4-methoxycarbonylphenyl)-1-methyl-pyrrole-3-carbonitrile (3.45g) was dissolved in tetrahydrofuran(30ml) under nitrogen atmosphere and then 2.0M lithium borohydride in tetrahydrofuran(12.8ml) was added to the solution at room temperature. The reaction mixture was stirred at 95 ℃ (reflux) for 4.5 hours, and cooled to 0℃ in ice-bath, saturated ammonium cholride was added dropwise to the mixture at 0 ℃ and stirred at 0 ℃ for 1 hour. The aqueous solution was extracted with ethyl acetate, and the organic layer was washed with water, saturated sodium bicarbonate and brine, dried

over magnesium sulfate and evaporated in vacuo. The residue was washed with diisopropyl ether-n-hexane to give 5-ethyl-2-(4-hydroxymethylphenyl)-1-methylpyrrole-3-carbonitrile (2.97g) as pale yellow solid.

mp : 71-75℃

NMR($CDCl_3$, δ): 1.30(3H,t, J=7.5Hz), 1.83(1H,br.t, J=5Hz), 2.60(2H,q J=7.5Hz), 3.48(3H,s), 4.76(2H,d, J=5Hz), 6.24(1H,s), 7.43(2H,d, J=9Hz), 7.50(2H,d, J=9Hz)

Preparation 11

5-Ethyl-2-(4-hydroxymethylphenyl)-1-methyl pyrrole-3-carbonitrile (1.47g), dichloromethane (15ml) and triethylamine (1.2ml) were combined under nitrogen atmosphere, and methanesufonyl chloride (497μ l) was added dropwise to the solution at -8℃ . The reaction mixture was stirred at -8 ℃ for 30 minutes. The organic layer was washed with water, saturated sodium bicarbonate and brine three times, dried over magnesium sulfate, and concentrated in vacuo to give 5-ethyl-2-(4-methanesulfonyloxymethylphehyl)-1-methylpyrrole-3-carbonitrile (2.05g) as pale yellow solid.

mp : 57-60℃

NMR($CDCl_3$, δ):1.30(3H,t, J=7.5Hz), 2.61(2H,qs,J=7.5Hz), 3.01(3H,s), 3.48(3H,s), 5.30(2H,s), 6.25(1H,s), 7.49(2H,d, J=9Hz), 7.55(2H,d, J=9Hz).

Preparation 12

To a solution of 5,7-dimethyl-2-propyl-3H-imidazo [4,5-b]pyridine (1.2g) in dimethylformamide (12ml) was added sodium hydride (253.6mg, 60% oil dispersion) at room temperature. The mixture was stirred at the same

temperature for 15 minutes. And a solution of 5-ethyl-1-methyl-2-(4-methanesulfonyloxymethylphenyl)pyrrole-3-carbonitrile (2.0 g) in dimethylformamide (12ml) was added dropwise to the mixture. The mixture was stirred at ambient temperature for 12 hours. The reaction mixture was poured into water and diluted with ethyl acetate. The mixture was extracted with ethyl acetate, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate was washed with water and saturated sodium chloride, and dried over magnesium sulfate. After filtration, the organic phase was concentrated in vacuo. The residue was purified by flash column chromatography (by ethyl acetate/n-hexane=1/1 → 2/1) and subsequent crystalligation from diisopropyl ether and the crystals
were collected by filtration and washed with diisopropyl ether to give pale yellow powder of 3-[4-(3-cyano-5-ethyl-1-methylpyrrol-2-yl)benzyl]-5, 7-dimethyl-2-propyl-3H-imidazo [4.5-b]pyridine (1.73g).
mp : 108-113℃
NMR ($CDCl_3$, δ) : 0.98(3H,t,J=7.5Hz),
1.29(3H,t,J=7.5Hz), 1.76(2H,m),
2.57(2H,q,J=7.5Hz), 2.60(3H,s), 2.64(3H,s),
2.77(2H,t,J=8Hz), 3.42(3H,s), 5.51(2H ,s),
6.21(1H,s), 6.90(1H,s), 7.21(2H,d,J=9Hz),
7.34(2H,d,J=9Hz)

Preparation 13

The following compounds were obtained according to a similar manner to that of Preparation 12.

5-Chloro-3-[4-(3-cyano-1-ethyl-5-methylpyrrol-2-yl)benzyl]-7-methyl-2-propyl-3H-imidazo[4.5-b]pyridine.
mp : 171-172℃
NMR ($CDCl_3$, δ) : 0.98(3H,t,J=7Hz),

1.17(3H,t,J=7Hz), 1.79(2H,m), 2.28(3H,s),
2.6 (3H,s), 2.80(2H,t,J=7Hz),
3.83(2H,q,J=7Hz), 5.50(2H,s), 6.21(1H,s),
7.09(1H,s), 7.21(2H,d,J=9Hz),
7.36(2H,d,J=9Hz)

Preparation 14

To a solution of 5-bromo-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine (2.26g) in dimethylformamide (10ml) was added sodium hydride (377mg) portionwise at room temperature. To the mixture was added a solution of 1-ethyl-5-methyl-2-(4-methanesulfonyloxymethylphenyl) pyrrole-3-carbonitrile (3.00g) in dimethylformamide (10ml) and the mixture was stirred for 3 hours. The reaction mixture was quenched with aqueous saturated ammonium chloride solution, and diluted with ethyl acetate. Water was added therein, and the crystals were collected by filtration.
The organic layer was separated and washed successively with saturated sodium cholride.
The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was triturated with ethyl acetate (30ml). The resulting crystals were collected by filtration. The combined crystals were poured into ethyl acetate (ca.150ml). After cooled to ambient temperature, the mixture quenched with ice water for one hour. The solid was collected by filtration and washed with cold ethanol. After drying in air, the solvent was evaporated to dryness under reduced pressure at 60℃ for 30 minutes to give 5-bromo-3-[4-(3-cyano-1-ethyl-5-methyl-2-pyrrolyl)benzyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b] pyridine (3.27g) as pale yellow powder.
mp : 201-204℃
NMR ($CDCl_3$, δ) : 1.16(3H,t,J=7.5Hz),

1.35(3H,t,J=8Hz), 2.27(3H,s),
2.65(3H,s), 2.83(2H,q,J=7.5Hz),
3.32(2H,q,J=7.5Hz), 5.49(2H,s), 6.20(1H,s),
7.21(2H,d,J=9Hz), 7.22(1H,s),
7.37(2H,d,J=9Hz)

Preparation 15

A mixture of 1-ethyl-5-methyl-2-(4-hydroxymethylphenyl)pyrrole-3-carbonitrile (1.0g) and trimethyltin azide(2.57g) in xylene(10ml) was stirred at 120℃ in an oil bath for 36 hours under nitrogen. The reaction mixture was concentrated in vacuo. The residue was dissolved in methanol(10ml). To the solution was added conc. hydrochloric acid (1ml) and the mixture was stirred at ambient temperature for an hour. The mixture was neutralized from 28% sodium methoxide-methanol and then adjusted to pH3, and evaporated in vacuo.
The residue was purified by flash column chromatography on silica gel (50g) (elution by chloroform ~ chloroform /methanol = 50/1) to yield 1-ethyl-2-(4-hydroxymethylphenyl)-5-methyl-3-(1H-tetrazol-5-yl)pyrrole (908mg) as colorless amorphous solid.

NMR ($CDCl_3$, δ) : 1.14(3H,t,J=7.5Hz), 2.33(3H,s),
3.76(2H,q,J=7.5Hz), 4.81(3H,s), 6.54(1H,s),
7.34(2H,d,J=8Hz), 7.57(2H,d,J=8Hz)

Preparation 16

A mixture of 1-ethyl-2-(4-hydroxymethylphenyl)-5-methyl-3-(1H-tetrazol-5-yl)pyrrole (903mg), trityl chloride (945mg), 10N aqueous sodium hydroxide (0.35ml), dichloromethane (8.9ml) and tetrahydrofuran (1.5ml) was stirred at ambient temperature for 12 hours. To the mixture was added trityl chlorid(390mg) and 10N sodium hydoroxide (0.14ml), and the mixture was

stirred at ambient temperature for 10 hours. The organic layer was separated and dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified with flash column chromatography on silica gel(elution by n-hexane /ethyl acetate = 3/1 ~ 2/1) to yield 1-ethyl-2-(4-hydroxymethylphenyl)-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)pyrrole (646mg) as white powder.

mp : 171-172℃

NMR ($CDCl_3$, δ) : 1.11(3H,t,J=7.5Hz), 2.34(3H,s), 3.78(2H,q,J=7.5Hz), 4.69(2H,d,J=5Hz), 6.55(1H,s), 6.85-7.04(7H,m), 7.09-7.39(12H,m)

Preparation 17

A solution of 1-ethyl-2-(4-hydroxymethylphenyl)-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)pyrrole (621mg), methanesulfonyl chloride (0.1ml) and trimethylamine (0.49ml) in dichloromethane (5ml) was stirred at 0℃ for 30 minutes and then at ambient temperature for 30 minutes. The solution was diluted with dichloromethane and washed with water, saturated sodium bicarbonate and saturated sodium chloride, and concentrated in vacuo. The residue was crystallized from diethyl ether, was washed with ethyl acetate (10ml) by supersonic waves. The filtrate was concentrated in vacuo.

The residue was purified by preparative thin layer chromatography on silica gel developed by ethyl acetate /n-hexane = 1/2 to give 2-(4-chloromethylphenyl)-1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-pyrrole (60mg) as white amorphous solid.

NMR ($CDCl_3$, δ) : 1.11(3H,t,J=7.5Hz), 2.34(3H,s), 3.77(2H,q,J=7.5Hz),

6.90-7.52(19H,m)

Preparation 18

A mixture of 5-bromo-2-ethyl-7-methylimidazo[4,5-b] pyridine(25.9g) and copper (I) cyanide (12.1g) in N,N-dimethylformamide (110ml) was refluxed for 23 hours. After cooled to room temperature, ethylenediamine (60ml) and water (200ml) were added to the mixture. The reaction mixture was stirred at room temperature for one hour. Ethyl acetate was added to the mixture, and filtered through a celite powder. The filtrate was separated, and the aqueous layer was neutralized with acetic acid and extracted with ethyl acetate (2 times). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/n-hexane to afford yellow solid. This solid was washed with diisopropyl ether to give 5-cyano-2-ethyl-7-methylimidazo[4,5-b]pyridine(108g) as a yellow solid.

mp : 212-213.5℃

NMR ($CDCl_3$, δ) : 1.52(3H,t,J=7.5Hz), 2.75(3H,s), 3.21(2H,q,J=7.5Hz), 7.50(1H,s)

Preparation 19

A mixture of 5-cyano-2-ethyl-7-methylimidazo[4,5-b] pyridine (11.7g) and 6N-hydrogen chloride (230ml) was refluxed for one hour. After cooled to room temperature, the mixture was concentrated in vacuo. The residue was washed with acetonitrile to give 5-carboxy-2-ethyl-7-methylimidazo[4,5-b]pyridine hydrochloride as an off-

white solid.
mp > 260℃
NMR (DMSO-d_6-D_2O, δ) : 1.42(3H,t,J=7.5Hz),
2.69(3H,s), 3.12(2H,q,J=7.5Hz),
8.02(1H,s)

Preparation 20

A mixture of 5-carboxy-2-ethyl-7-methylimidazo-[4,5-b]pyridine hydrochloride (18.3g) and concentrated sulfuric acid (18ml) in ethanol (180ml) was refuluxed for 1.5 hours under nitrogen atmosphere. After cooled to room temperature, the mixture was concentrated in vacuo.
The residue was dissolved in ethyl acetate, and the solution was neutralized with saturated sodium bicarbonate. The mixture was separated, and the aqueous layer was extracted with ethyl acetate (2 times).
The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was washed with diisopropyl ether to give 5-(ethoxycarbonyl)-2-ethyl-7-methylimidazo-[4,5-b]pyridine (12.4g) as a pale yellow solid.
mp : 155-163℃
NMR ($CDCl_3$, δ) : 1.41(3H,t,J=7.5Hz),
1.47(3H,t,J=7.5Hz), 2.75(3H,s),
3.18(2H,q,J=7.5Hz), 4.50(2H,q,J=7.5Hz),
7.91(1H,s)

Preparation 21

5-(Ethoxycarbonyl)-2-ethyl-7-methylimidazo-[4,5-b]pyridine (3.7g) was dissolved in 75ml of dimethylformamide under nitrogen atmosphere and sodium hydride (634.5mg) was added portionwise to the solution at room temperature. The mixture was stirred at room temperature for 1hour, and 5-ethyl-1-methyl-2-(4-

methanesulfonyloxymethylphenyl)pyrrole-3-carbonitrile (5g) was added portionwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 1 hour, and poured into water. The aqueous solution was extracted with ethyl acetate (three times), and the combined organic layers were washed with brine, dried over magnesium sulfate and evaporated.
The residue was purified by silica gel column chromatography to afford a solid.
(ethyl acetate : n-hexane = 2:1) (6.09g) The solid was washed with diisopropyl ether to give 3-[4-(3-cyano-1-ethyl-5-methyl-2-pyrrolyl)benzyl]-5-ethoxycarbonyl-2-ethyl-7-methyl-3H-imidazo[4,5-b]-pyridine (5.87g) as a white solid.
mp : 162-165℃
NMR($CDCl_3$, δ) : 1.13(3H,t,J=7.5Hz),
1.39(3H,t,J=7.5Hz), 1.46(3H,t,J=7.5Hz),
2.28(3H,s), 2.75(3H,s), 2.88(2H,q,J=7.5Hz),
3.81(2H,q, J=7.5Hz), 4.47(2H,q, J=7.5Hz),
5.62(2H,s), 6.21(1H,s), 7.23(2H,d,J=9.0Hz),
7.36(2H,d,J=9.0Hz), 7.95(H,s).

Example 1

A mixture of 3-[4-(3-cyano-1,5-diethyl-2-pyrrolyl)-benzyl]-5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridine (1.625g) and trimethyltin azide (2.36g) in xylene (15ml) was stirred at 130℃ for 4 days. The mixture was diluted with methanol (15ml) and conc. hydrochloric acid (1.1ml) was added therein. The mixture was stirred for 30 minutes, and then evaporated in vacuo. The residue was dissolved in methanol (15ml) and adjusted to pH4 with aqueous 5N sodium hydroxide. The organic layer was separated, and evaporated in vacuo. The residue was dissolved in 15%

methanol-chloroform, dried over magnesium sulfate, and filtered. The filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (elution by chloroform → 3% methanol/chloroform → 5% methanol/chloroform), and subsequent combined fraction was evaporated. The residue was crystallized from ether on standing overnight. The resulting precipitate was collected by filtration. The precipitate was air-dried at room temperature, and recrystallized from ether to give 3-[4-[1,5-diethyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl] benzyl]- 5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]-pyridine (1.00g) as pale yellow powder.

mp : 159-162℃

NMR (DMSO-d_6, δ) :

0.86(3H,t,J=7.5Hz), 0.96(3H,t,J=7.5Hz),
1.27(3H,t,J=7.5Hz), 1.65(2H,m), 2.50 (3H × 2,s),
2.65(2H,q,J=7.5Hz), 2.76(2H,t,J=8Hz),
3.73(2H,br,q,J=7.5Hz),
5.53(2H,s), 6.36(1H,s), 6.95(1H,s),
7.17(2H,d,J=9Hz), 7.28(2H,d,J=9Hz)

Example 2

To a solution of 3-[4-[1,5-diethyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5,7-dimethyl-2-propyl-3H-imidazo-[4,5-b]-pyridine (977mg) in water (5ml) was added 1N sodium hydroxide (2ml). The mixture was stirred at 90 ℃ for 5 minutes. The precipitate was collected by filtration and dissolved in ethanol. The solvent was evaporated in vacuo. The residue was crystallized from 99% acetronitrile to give sodium salt of 3-[4-[1,5-diethyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridine (676mg) as pale brown powder.

mp : 168-172℃

NMR (DMSO-d_6, δ) : 0.89(3H,t,J=7.5Hz),
0.95(3H,t,J=7.5Hz), 1.26(3H,t,J=7.5Hz),
1.68(2H,m), 2.50 (3H× 2,s),2.60(2H,m),
2.77(2H,t,J= Hz), 3.70(2H,q,J=7.5Hz),
5.48(2H,s), 6.12(1H,s), 6.95(1H,s),
7.07(2H,d,J=9Hz), 7.31(2H,d,J=9Hz)

Example 3

To a stirred solution of 3-[4-(3-cyano-5-ethyl-1-methyl-2-pyrrolyl)benzyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (1.66g) in xylene (16ml) was added trimethyltin azide (2.49g), and stirred for 76 hours. The mixture was diluted with methanol (15ml) and conc. hydrochloric acid (1.5ml) was added therein. The mixture was stirred at room temperature for 30 minutes, and evaporated in vacuo. The residue was diluted with methanol (15ml) and adjusted to pH4~5 with 5N sodium hydroxide and evaporated in vacuo. The residue was dissolved in 15% methanol/chloroform, and dried over magnesium sulfate and evaporated. The residue was purified by flash column chromatography elution by chloroform~3% methanol/chloroform~5% methanol/chloroform, and subsequent combined fraction was evaporated in vacuo. The residue was poured into diethyl ether (30ml) and allowed to stand for two days. The resulting precipitate was collected by filtration. The precipitate was crystallized from acetonitrile (30ml) to give 5,7-dimethyl-3-[4-[5-ethyl-1-methyl-3-(1H-tetrazol-5-yl)pyrrolyl]benzyl]-2-propyl-3H-imidazo[4,5-b]pyridine (982mg) as white powder.

mp : 202-205℃

NMR (DMSO-d_6, δ) : 0.89(3H,t,J=7.5Hz),
1.24(3H,t,J=7.5Hz), 1.70(2H,m),
2.49 (3H× 2,each s), 2.62(2H,q,J=7.5Hz),

2.78(2H,t,J=8Hz), 3.32(2H,s), 5.54(2H,s),
6.36(1H,s), 6.97(1H,s), 7.18(2H,d,J=9Hz),
7.31(2H,d,J=9Hz)

Example 4

The following compound was obtained according to a similar manner to that of Example 2.

Sodium salt of 5,7-dimethyl-3-[4-[5-ethyl-1-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-2-propyl-3H-imidazo-[4,5-b]pyridine.

mp : 171-177℃

NMR (DMSO-d_6, δ) : 0.91(3H,t,J=7.5Hz),
1.23(3H,t,J=7.5Hz), 1.72(2H,m),
2.52 (3H× 2,each s), 2.58(2H,q,J=7.5Hz),
2.77(2H,t,J=8Hz), 3.29(3H,s), 5.49(2H,s),
6.11(1H,s), 6.95(1H,s), 7.05(2H,d,J=9Hz),
7.37(2H,d,J=9Hz)

Example 5

The following compound was obtained according to a similar manner to that of Example 1.

5-Chloro-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]-pyridine.

mp : 137-139℃

NMR (DMSO-d_6, δ) :
0.89(3H,t,J=7Hz), 1.01(3SH,t,J=7Hz), 1.68(2H,m),
2.30(3H,s), 2.58(3H,s), 3.73(2H,q,J=7Hz),
5.54(2H,s), 6.35(1H,s), 7.19(2H,d,J=8Hz),
7.22(1H,s), 7.32(2H,d,J=8Hz)

Example 6

To a solution 5-chloro-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine (285mg) in water (3ml) was

added 1N sodium hydroxide (0.6ml) and lyophilized to afford sodium salt of 5-chloro-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine.

NMR (D_2O, δ) :

0.54(3H,t,J=7Hz), 0.66(3H,t,J=7Hz),
1.38(2H,m), 1.97(3H,s), 2.22(3H,s),
2.66(2H,t,J=7Hz), 3.21(2H,q,J=7Hz),
5.20(2H,s), 6.27(1H,s), 6.57(1H,s),
6.90(2H,d,J=8Hz), 6.98(2H,d,J=8Hz)

Example 7

A mixture of 5-bromo-3-[4-(3-cyano-1-ethyl-5-methyl-2-pyrrolyl)benzyl]-7-methyl-2-ethyl-3H-imidazo-[4,5-b]pyridine (3.00g) and trimethyltin azide (4.01g) in xylene (30ml) was stirred at 130 ℃ for 64.5 hours and further more trimethyltin azid (1.33g) was added therein. The mixture was stirred overnight at the same temperature.

To the mixture was added conc. hydrochloric acid (2.5ml) and methanol (15ml), and stirred at room temperature for one hour and evaporated in vacuo. The residue was dissolved in methanol (15ml) and adjusted to pH5 with 1N sodium hydroxide. The solvent was removed in vacuo and the residual water was removed azeotropically with toluene-methanol. The residue was dissolved in 15% methanol-chloroform, and evaporated in vacuo, dried over magnesium sulfate. The residue was purified by column chromatography on silica gel (15g) (elution by chloroform then 3% methanol/chloroform). The combined fraction was evaporated in vacuo and crystallized from added methyl cyanide. The resulting precipitate was collected by filtration. The precipitate was suspended in ethanol (ca. 200ml). The mixture was allowed to heat to 90 ℃ for 10 minutes.

The mixture was allowed to stand to room tenperature with stirring. After the mixture was stirred under ice cooling for 30 minutes, the resulting solid collected by filtration, was washed with ethanol to give 5-bromo-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrroyl]benzyl]-7-methyl-3H-imidazo [4,5-b]pyridine (2.322g) as pale yellow powder.

mp : 249-254℃

NMR (DMSO-d_6, δ) : 1.00(3H,t,J=7.5Hz), 1.23(3H,t,J=7.5Hz), 2.29(3H,s), 2.57(3H,s), 2.85(2H,q,J=7.5Hz), 3.73(2H,br,q,J=7.5Hz), 5.53(2H,s), 6.34(1H,s), 7.19(2H,d,J=9Hz), 7.31(2H,d,J=9Hz), 7.34(1H,s)

Example 8

To a suspension of 5-bromo-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrroyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (200mg) in water (2ml) was added 1N sodium hydroxide (0.39ml). The mixture was stirred at 90 ℃ for 3 minutes, clarified by sonication, and the solution was filtered through a milipor filter. The filtrate was lyophilized to yield sodium salt of 5-bromo-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo [4,5-b]pyridine(180mg) as white powder.

NMR (DMSO-d_6, δ): 0.97(3H,t,J=7.5Hz), 1.25(3H,t,J=7.5Hz), 2.25(3H,s), 2.57(3H,s), 2.84(2H,q,J=7.5Hz), 3.69(2H,q,J=7.5Hz), 5.47(2H,s), 6.10(1H,s), 7.09(2H,d,J=9Hz), 7.32(1H,s), 7.34(2H,d,J=9Hz)

Example 9

A mixture of 5-bromo-2-ethyl-3-[4-[1-ethyl-5-methyl

-3-(1H-tetrazol-5-yl)2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine(400mg) and sodium methoxide(28% solution in methanol)(5ml)was refluxed for 10 hours. After being cooled,the mixture was neutralized with conc. hydrochloric acid and extracted with chloroform (3 times). The organic layer was dried over anhydrous magnesium sulfate, concentrated in vacuo to give an amorphous solid. The solid was solidified with 99% acetonitrile, filtered and then recrystallized from the same solvent to afford 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)2-pyrrolyl]benzyl]-5-methoxy-7-methyl-3H-imidazo[4,5-b]pyridine (212mg) as a white powder.

mp : 213-215℃

NMR (DMSO-d_6, δ) : 1.01(3H,t,J=7.5Hz),
1.21(3H,t,J=7.5Hz), 2.30(3H,s),
2.82(2H,q,J=7.5Hz), 3.71(2H,br,q,J=7.5Hz),
3.89(3H,s), 5.49(2H,s), 6.35(1H,s),
6.53(1H,s), 7.30(4H,s)

Example 10

To a suspension of 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)2-pyrrolyl]benzyl]-5-methoxy-7-methyl-3H-imidazo[4,5-b]pyridine (205mg) in water (2ml) was added 1N sodium hydroxide (0.45ml). The mixture was heated at 90℃ , and lyophilized to yield sodium salt of 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-methoxy-7-methyl-3H-imidazo [4,5-b]pyridine (192mg) as a white solid.

NMR (DMSO-d_6, δ) : 0.97(3H,t,J=7.5Hz),
1.21(3H,t,J=7.5Hz), 2.25(3H,s), 2.49(3H,s),
2.80 (2H,q,J=7.5Hz) 3.68(2H,br,q,J=7.5Hz),
3.89(3H,s), 5.43(2H,s), 6.10(1H,s),
6.51(1H,s), 7.16(2H,d,J=9Hz) 7.33(2H,d,J=9Hz)

Example 11

To a solution of 5-cyano-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine (107mg) in dimethylformamide (1ml) was added sodium hydride (23mg) and the mixture was stirred at room temperature for 30 minutes.
To the mixture was added a suspension of 1-ethyl-2-(4-chloromethylphenyl)-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)pyrrole (260mg) in dimethylformamide and tetrabutylammonium iodide (catalytic amounts). The mixture was stirred at the same temperature for 27 hours and then quenched with aqueous ammonium chloride and extracted with chloroform. The organic layer was dried over magnesium sulfate to give brown solid. The solid was poured into ethyl acetate and allowed to heated to 90 ℃ .
After being allowed to stand to room temperature, the resulting precipitate was collected by filtration and washed to give 5-cyano-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]-benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (250mg) as pale brown solid.
mp : 186-192℃
NMR ($CDCl_3$, δ) :
1.08(3H,t,J=7.5Hz), 1.25(3H,5,J=7.5Hz),
2.30(3H,s), 2.52(3H,s), 2.80(3H,q,J=7.5Hz),
3.53(2H,br,q,J=7.5Hz), 5.94(2H,s), 6.54(1H,s),
6.88~9.52(19H,m)

Example 12

5-cyano-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]-benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (201mg) and 80% acetic acid (3ml) were combined. The reaction mixture was stirred at 60 ℃ for an hour, and

concentrated in vacuo with toluene (three times). The residue was purified by flash column chromatography (eluent: ethyl acetate) to give a yellow solid. The solid was crystallized from 99% acetonitrile and recrystallized from 99% acetonitrile to give 5-cyano-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (44mg) as white powder.

mp : 211-214℃

NMR (DMSO-d_6, δ) :

1.01(3H,t,J=7.5Hz), 1.26(3H,t,J=7.5Hz), 2.30(3H,s), 2.63(3H,s), 2.94(2H,q,J=7.5Hz), 3.73(2H,br,q,J=7.5Hz), 5.60(2H,s), 6.86(1H,s), 7.23(2H,d,J=9Hz), 7.32(2H,d,J=9Hz),7.78(1H,s)

Example 13

The following compound was obtained according to a similar manner to that of Example 10.

Sodium salt of 5-cyano-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine.

NMR (DMSO-d_6, δ) :

0.98(3H,t,J=7.5Hz), 1.27(3H,t,J=7.5Hz), 2.24(3H,s), 2.62(3H,s), 2.93(2H,q,J=7.5Hz), 3.69(2H,q,J=7.5Hz), 5.55(2H,s), 6.10(1H,s), 7.11(2H,d,J=9Hz), 7.33(2H,d,J=9Hz),7.75(1H,s)

Example 14

3-[4-(3-Cyano-1-ethyl-5-methyl-2-pyrrolyl)benzyl]-5-ethoxycarbonyl-2-ethyl-7-methyl-3H-imidazo[4,5-b] pyridine (5.4g), trimethyltin azide (7.3g) and xylene (45ml) were combined under nitrogen atmosphere, and the mixture was stirred at 130℃ for 52 hours. After cooled to room temperature, conc. hydrochloric acid (9ml) and ethanol (25ml) were added to the mixture, and stirred

at room temperature for 30 minutes. The solution was concentrated in vacuo, and the residue was dissolved in ethanol. 1N sodium hydroxide was added to the mixture until pH=4, and concentrated in vacuo. The residue was purified silica gel column chromatography (eluted by chloroform → methanol/chloroform = 1:3 → ethyl acetate/acetic acid = 20:1) to yield 2-ethyl-3-[4-[1-ethyl-5-methyl-3-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-ethoxycarbonyl-7-methyl-3H-imidazo-[4,5-b]pyridine (885.6mg) as a pale yellow solid.

mp. 106-114 ℃

NMR(DMSO-d_6, δ):

1.03(3H,t, J=7.5Hz), 1.24(3H,t, J=7.5Hz),
1.35(3H,t, J=7.5Hz), 2.30(3H,s), 2.65(3H,s),
2.89(2H,q, J=7.5Hz), 3.73(2H,q, J=7.5Hz),
4.35(2H,q, J=7.5Hz), 5.62(2H,s), 6.33(1H,s),
7.21(2H,d, J=9.0Hz), 7.31(2H,d, J=9.0Hz),
7.91(1H,s).

Example 15

2-Ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-ethoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (199.8mg) was dissolved in 2ml of ethanol and then 1N sodium hydroxide (400.7ml) and 1ml of water were added to the solution. The mixture was filtered through a millipore filter and the filtrate was concentrated in vacuo. The residue was dissolved in 5ml of water and lyophilized to yield sodium salt of 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-ethoxycarbonyl-7-methyl-3H-imidazo [4,5-b]pyridine (182.1mg) as pale yellow powder.

NMR(DMSO-d_6, δ):

0.99(3H,t, J=7.5Hz), 1.27(3H,t, J=7.5Hz),
1.36(3H,t, J=7.5Hz), 2.25(3H,s), 2.64(3H,s),
2.90(2H,q, J=7.5Hz), 3.69(2H,q, J=7.5Hz),

4.38(2H,q, J=7.5Hz), 5.58(2H,s), 6.11(1H,s),
7.12(2H,d, J=9.0Hz), 7.36(2H,d, J=9.0Hz),
7.90(1H,s).

Example 16

2-Ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-ethoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (201.8mg) was dissolved in 2ml of ethanol, and then 1N sodium hydroxide (1.5ml) was added to the solution. The reaction mixture was stirred at 90 ℃ under reflux for 1 hour. After cooled to room temperature, the mixture was concentrated in vacuo. The residue was dissolved in water and 1N hydrochloric acid was added to the solution until pH4. The solid was filtered off. The solid was washed with acetonitrile to give
5-carboxy-2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b] pyridine (52.7mg) as white solid.
mp. 174-180 ℃
NMR(DMSO-d_6, δ):
1.00(3H,t, J=7.5Hz), 1.25(3H,t, J=7.5Hz),
2.28(3H,s), 2.62(3H,s), 2.89(2H,q, J=7.5Hz),
3.72(2H,q, J=7.5Hz), 5.63(2H,s), 6.33(1H,s),
7.20(2H,d, J=9.0Hz), 7.31(2H,d, J=9.0Hz),
7.88(1H,s).

Example 17

5-Carboxy-2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo [4,5-b] pyridine (40.4mg), water (0.5ml) and 1N sodium hydroxide (171.7μ l) were combined, and dissolved. The mixture was filtered through a millipore filter. The filtrate was lyophilized to yield disodium salt of 5-carboxy-2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-

b] pyridine (39.7mg) as white powder.

NMR(D_2O, δ):

0.99(3H,t, J=7.5Hz), 1.20(3H,t, J=7.5Hz),
2.30(3H,s), 2.67(3H,s), 2.90(2H,q, J=7.5Hz),
3.71(2H,q, J=7.5Hz), 5.68(2H,s), 6.36(1H,s),
7.21(4H,s), 7.80(1H,s).

Example 18

2-Ethyl-3-[4-[1-ethyl-5-methyl-3-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-ethoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (50mg) was dissolved in 1ml of tetrahydrofuran under nitrogen atmosphere and then lithium aluminum hydride (19mg) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 minutes.
Methanol was added to the solution, and then 1N sodium hydroxide (1.5ml) was added to the mixture.
The suspension was stirred at room temperature for 1 hour, and filtered through a celite powder.
The celite was washed with methanol chloroform=1:5.
The filtrate was concentrated in vacuo. Methanol was added to the residue, and 1N hydrochroric acid was added to the solution until pH4. The organic solvent was evaporated in vacuo to give
2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5- hydroxymethyl-7-methyl-3H-imidazo[4,5-b]pyridine
(27.6m g) as white solid.
mp. 273-275 ℃

NMR(DMSO-d_6, δ):

1.03(3H,t, J=7.5Hz), 1.23(3H,t, J=7.5Hz),
2.30(3H,s), 2.59(3H,s), 2.83(2H,q, J=7.5Hz),
3.72(2H,q, J=7.5Hz), 4.62(2H,s), 5.56(2H,s),
6.34(1H,s), 7.17(2H,d, J=9.0Hz), 7.21(1H,s),
7.30(2H,d, J=9.0Hz).

Example 19

2-Ethyl-3-[4-(1-ethyl-5-methyl-3-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-hydroxymethyl-7-methyl-3H-imidazo[4,5-b]pyridine (17.6mg), 1N sodium hydroxide (38.6ml) and water (0.5ml) were combined, and dissolved. The mixture was filtered through a millipore filter. The filtrate was lyophilized to yield sodium salt of 2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]-benzyl]-5-hydroxymethyl-7-methyl-3H-imidazo[4,5-b] pyridine(19.1mg) as white powder.

NMR(DMSO-d_6, δ):

0.78(3H,t, J=7.0Hz), 1.04(3H,t, J=7.5Hz), 2.03(3H,s), 2.38(3H,s), 2.62(2H,q, J=7.5Hz), 3.48(2H,q, J=7.0Hz), 4.41(2H,s), 5.19(1H,bs), 5.29(2H,s), 5.90(1H,s), 6.68(2H,d, J=8.5Hz), 7.00(1H,s), 7.12(2H,d, J=8.5Hz).

Example 20

A mixture of 5-carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (1.50g), trityl chloride (711mg) and triethylamine (700μ 1) in dichloromethane (20ml) was stirred for 3.5 hours.

The reaction mixture was diluted with chloroform and the solution was washed with water and saturated sodium chloride, and dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluted with a mixture of 3% methanol/chloroform then with 5% methanol /chloroform, and subsequent triturated with diisopropyl ether and collected by filtration and washed with ethanol. The solid was collected by filtration to give 5-carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-

methyl-3H-imidazo[4,5-b]pyridine (800mg) as pale brown solid.

mp : 144-148℃

NMR ($CDCl_3$-CD_3OD 1:1 v/v, δ) :

1.07 (3H,t,J=7.5Hz), 1.21 (3H,t,J=7.5Hz),
2.33 (3H,s), 2.74 (2H,q,J=7.5Hz), 2.77 (3H,s),
3.75 (2H,q,J=7.5Hz), 5.60 (2H,s), 6.50 (1H,s),
6.82-7.36 (19H,m), 8.04 (1H, s).

Example 21

To a stirred suspension of 5-carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2 -pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]-pyridine (250mg) in tetrahydrofuran (5ml) was added triethylamine (290μ l) and ethyl chloroformate(100μ l) in an ice-water bath. The mixture was stirred at the same temperature for 15 minutes, and then at ambient temperature for half an hour. Methylamine (30% solution in water) (5ml) was added to the mixture and the resulting heterogeneous mixture was stirred for one and half hours. The mixture was diluted with chloroform and water and the organic phase was washed with water and saturated sodium chloride. After being dried over anhydrous magnesium sulfate, the solvent was removed in vacuo. The pinkish residue was chromatographed on silica gel eluting with a mixture of methanol and chloroform (3 : 97) to give 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-N-methyl-7-methyl-3H-imidazo[4,5-b] pyridine-5-carboxamide (141mg) as a pale yellow powder.

mp : 205-211℃

NMR ($CDCl_3$, δ):

1.07 (3H,t,J=7.5Hz), 1.26 (3H,t,J=7.5Hz),
2.31 (3H,s), 2.76 (3H,s), 2.78 (2H,q,J=7.5Hz),
2.98 (3H,d,J=6Hz), 3.73 (2H,q,J=7.5Hz),

5.46 (2H,s), 6.51 (1H,s), 6.90-7.09 (7H,m),
7.13-7.35 (12H,m), 7.85 (1H,br,q,J=6Hz),
8.05 (1H,s).

Example 22

A solution of 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]-benzyl]-N-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide (135mg) in a mixture of 1N hydrochloric acid (0.5ml) and methanol (4.5ml) was stirred at ambient temperature for 10 minutes and then at 60 ℃ for 30 minutes. After cooling, the solution was neutralized by addition of 1N sodium hydroxide and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (2 m/m thickness, 2 plates, 20cm× 20cm) (methanol/chloroform 7/93) to give colorless amorprous solid which was solidified with chloroform. The solid was filtered and washed with ethyl acetate to give 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-N-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide (60mg) as a white powder.

mp : 249-254℃

NMR (DMSO-d6, δ):
1.00 (3H,t,J=7.5Hz), 1.20 (3H,t,J=7.5Hz),
2.28 (3H,s), 2.61 (3H,s), 2.84 (3H,d,J=5Hz),
2.84 (2H,q,J=7.5Hz), 3.73 (2H,br,q,J=7.5Hz),
5.71 (2H,s), 6.34 (1H,s), 7.24 (2H,d,J=9Hz),
7.30 (2H,d,J=9Hz), 7.83 (1H,s),
8.82 (1H,br,q,J=5Hz)

Example 23

The following compound was obtained according to a similar manner to that of Example 8.

Sodium salt of 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-N-methyl-3H-

imidazo [4,5-b]pyridine-5-carboxamide.

NMR (DMSO-d_6, δ):

0.97 (3H,t,J=7.5Hz), 1.24 (3H,t,J=7.5Hz),
2.25 (3H,s), 2.63 (3H,s), 2.85 (3H,d,J=6Hz),
2.85 (2H,q,J=7.5Hz), 3.69 (2H,q,J=7.5Hz),
5.65 (2H,s), 6.10 (1H,s), 7.10 (2H,d,J=9Hz),
7.33 (2H,d,J=9Hz), 7.83 (1H,s),
8.82 (1H,br,q,J=6Hz)

Example 24

5-Carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (100mg), dichloromethane (1ml), 4-dimethylaminopyridine (20mg), methanesulfonamide (14.7mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.6mg), were combined at 0 ℃ under nitrogen atmosphere. The reaction mixture was stirred at 0 ℃ and then at room temperature for 4 hours. Chloroform and water were added to the solution, and separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel developed by methanol/dichloromethane =1/10 to yield a white solid.The white solid, ethanol(7ml) and 4N hydrochloric acid-dioxane (0.2ml) were combined, and stirred at room temperature for 30 minutes. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethanol. 1N sodium hydroxide was added to the solution until pH5. The mixture was concentrated in vacuo. The residue was purified by preparative thin chromatography on silica gel developed by methanol/ dichloromethane = 1:10 to yield 2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-

methanesulfonamidocarbonyl-7-methyl-3H-imidazo[4,5-b]-pyridine (14.4mg) as amorphous solid.

NMR($CDCl_3$, δ):

1.09(3H,t,J=7.5Hz), 1.37(3H,t,J=7.5Hz),
2.28(3H,s), 2.74(3H,s), 2.88(2H,q, J=7.5Hz),
3.41(3H,s), 3.71(2H,q,J=7.5Hz), 5.50(2H,s),
6.47(1H,s), 7.10(2H,d,J=8.0Hz),
7.24(2H,d, J=8.0Hz), 8.02(1H,s).

Example 25

2-Ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-methanesulfonamidocarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (14.4mg), 1N sodium hydroxide (26.3ml) and water (0.5ml) were combined, and dissolved. The mixture was filtered through a millipore filter. The filtrate was lyophilized to yield sodium salt of 2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-methanesulfonamidocarbonyl-7-methyl-3H-imidazo[4,5-b]-pyridine (15.0mg) as solid.

NMR (DMSO-d_6, δ):

0.97 (3H,t,J=7.5Hz), 1.26 (3H,t,J=7.5Hz),
2.23 (3H,s), 2.59 (3H,s), 2.81 (2H,q,J=7.5Hz),
2.88 (3H,s), 3.68 (2H,q,J=7.5Hz), 5.59 (2H,s),
6.10 (1H,s), 7.07 (2H,d,J=8.5Hz),
7.33 (2H,d,J=8.5Hz), 7.87(1H,s)

Example 26

5-Carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]-7-methyl-3H-imidazo[4,5-b]pyridine (100mg), N,N-dimethylformamide (1ml), 1-hydroxybenzotriazole (21mg), L-phenylalanine ethyl ester hydrochloride(35.5mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (24mg) were combined at 0℃ under nitrogen atmosphere. The reaction mixture

was stirred at room temperature for 3 hours. Ethyl acetate and water were added to the solution, and the mixture was separated.The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel eluting with methanol/dichloromethane to give N-[{2-Ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo-[4,5-b]pyridin-5-yl}carbonyl]-L-phenylalanine ethyl ester (77.3mg) as a white solid.

mp : 169-171 ℃

NMR ($CDCl_3$, δ):

1.06 (3H,t,J=7.5Hz), 1.21 (3H,t,J=7.5Hz),
1.24 (3H,t,J=7.5Hz), 2.30 (3H,s),
2.73 (2H,q,J=7.5Hz), 2.77 (3H,s),
3.21 (2H,d,J=6.0Hz), 3.71 (2H,q,J=7.5Hz),
4.16 (2H,q,J=7.5Hz), 4.98-5.12 (1H,m),
5.29 (1H,d,J=15.5Hz), 5.50 (1H,d,J=15.5Hz),
6.53 (1H,s), 6.91-7.02 (6H,m),
7.05-7.34 (18H,m), 8.02 (1H,s),
8.39 (1H,d,J=8.5Hz)

Example 27

N-[{2-Ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridin-5-yl}carbonyl]-L-phenylalanine ester (71.2mg), ethanol (7ml) and 4N hydrochloric acid-dioxane (0.2ml) were combined, and stirred at room temperature for 30 minutes. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethanol. 1N sodium hydroxide was added to the solution until pH5. The mixture was concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel developed by methanol/dichloromethane (1/10) to give

N-[{2-Ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-yl}carbonyl]-L-phenylalanine ethyl ester (54.5mg) as amorphous.

NMR ($CDCl_3$, δ):

1.09 (3H,t,J=7.5Hz), 1.21 (3H,t,J=7.5Hz),
1.40 (3H,t,J=7.5Hz), 2.30 (3H,s),
2.71 (3H,s),
2.96 (2H,q,J=7.5Hz), 3.26 (2H,d,J=6.0Hz),
3.70 (2H,q,J=7.5Hz), 4.15 (2H,q,J=7.5Hz),
5.00-5.13 (1H,m),
5.46 (2H,s), 6.54 (1H,s),
7.17 (5H,s), 7.25 (4H,s),
7.99 (1H,s), 8.40 (1H,d,J=8.0Hz)

Example 28

N-[{2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo-[4,5-b]pyridin-5-yl}carbonyl]-L-phenylalanine ethyl ester (52.8mg), 1N sodium hydroxide (81.8 μ l) and water (0 .5ml) were combined, and dissolved. The mixture was filtered through a millipore filter. The filtrate was lyophilized to yield sodium salt of N-[{2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl] benzyl]-7-methyl-3H-imidazo[4,5-b]-pyridin-5-yl}carbonyl]-L-phenylalanine ethyl ester (14.2 mg) as solid.

NMR (DMSO-d_6, δ):

0.97 (3H,t,J=7.5Hz), 1.15 (3H,t,J=7.5Hz),
1.26 (3H,t,J=7.5Hz), 2.25 (3H,s), 2.61 (3H,s),
2.89 (2H,q,J=7.5Hz), 3.23 (2H,d,J=7.0Hz),
3.71 (2H,q,J=7.5Hz), 4.12 (2H,q,J=7.5Hz),
4.67-4.83 (1H,m), 5.64 (2H,s), 6.15 (1H,s),
7.02-7.40 (9H,m), 7.79 (1H,s),
8.86 (1H,d,J=7.5Hz)

Example 29

A mixture of N-[{2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridin-5-yl}carbonyl]-L-phenylalanine ethyl ester (112mg), 1N sodium hydroxide (0.35ml) and ethanol (3ml) was stirred at ambient temperature for 1.5 hours. The solvent was evaporated in vacuo. The residue was diluted with water (3ml), and 1N hydrochloric acid was added to the residue until pH5. The resulting precipitate was collected by filtration, and washed with water and triturated with ether (3ml). The solid was collected by filtration and evaporated in vacuo at 70 ℃ for 2 hours to give N-[[2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo-[4,5-b]pyridin-5-yl]carbonyl]-L-phenylalanine (55mg) as white powder.

mp : 172-178 ℃

NMR (DMSO-d6, δ):

1.00 (3H,t,J=7.5Hz), 1.25 (3H,t,J=7.5Hz),
2.29 (3H,s), 2.60 (3H,s), 2.90 (2H,q,J=7.5Hz),
3.22 (2H,d,J=6Hz), 3.72 (2H,br,q,J=7.5Hz),
4.68 (1H,dt,J=8 and 6Hz), 5.61 (1H,d,J=12.5Hz),
5.70 (1H, dt, J=12.5Hz), 6.35 (1H, s),
7.06 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz),
7.17-7.35 (5H,m), 7.78 (1H,s),
8.75 (1H, d, J=8Hz).

Example 30

5-Carboxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (200mg) was dissolved in 4ml of tetrahydrofuran under nitrogen atmosphere, and triethylamine (233.5μ l) and ethylchlorocarbonate

(80.5 μl) were added to the solution at 0℃. The reaction mixture was stirred at room temperature for 1 hour, and then hydroxymethylamine·hydrochloride (46.9mg) was added to the mixture.
The reaction mixture was stirred at room temperature for 1.5 hours. Water was added to the mixture, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to give a crude product (205.2mg). The product, ethanol (2ml) and 4N hydrochloric acid-dioxane (0.1ml) were combined under nitrogen atmosphere, and stirred at room temperature for 30 minutes. The mixture was concentrated in vacuo, and dissolved in methanol. The solution was neutralized with 1N sodium hydroxide, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel developed by methanol/dichloromethane (1/7) to give 7,N-dimethyl-2-ethyl-3-[2-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-3H-imidazo[4,5-b]-pyridine-5-carbohydroxamic acid (48.1mg) as brownish powder.

mp : 125-130℃

NMR ($CDCl_3$, δ):
1.11 (3H,t,J=7Hz), 1.52 (3H,t,J=7Hz),
2.32(3H,s), 2.75 (3H,s), 3.10 (2H,q,J=7Hz),
3.44(3H,s), 3.74 (2H,q,J=7Hz), 5.48 (2H,s),
6.62(1H,s), 7.16-7.40 (4H), 7.98 (1H,s)

Example 31

The following compound was obtained according to a similar manner to that of Example 28.

Disodium salt of 7,N-dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-3H imidazo[4,5-b]pyridine-5-carbohydroxamic acid.

NMR(D_2O, δ):

0.99(3H,t, J=7Hz), 1.23(3H,t, J=7Hz), 2.30(3H,s),
2.67 (3H,s), 2.96(2H,q, J=7Hz), 3.09(2H,s),
3.42(1H,s), 3.73 (2H,q, J=7Hz), 5.61(2H br s),
6.36(1H,s), 7.10-7.28(4H), 7.35(1H,s)

Example 32

The following compound was obtained according to a similar manner to that of Example 9.

5-Ethoxy-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]]benzyl]-7-methyl-3H-imidazo-[4,5-b]pyridine.

mp.156-162℃

NMR(DMSO-d_6, δ):

1.00(3H,t, J=7.5Hz), 1.22(3H,t, J=7.5Hz),
1.31(3H,t, J=7.0Hz), 2.29(3H,s), 2.53(3H,s),
2.82(2H,q, J=7.5Hz), 3.71(2H,q, J=7.5Hz),
4.34(2H,q, J=7.0Hz), 5.46(2H,s),
6.32(1H,s), 6.50(1H,s), 7.28(4H,s).

Example 33

5-Ethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo [4,5-b]pyridine (105mg), 1N sodium hydroxide (223.1 μ l) and water (1ml) were combined, and dissolved. The mixture was filtered through a millipore filter, and the filtrate was lyophilized to yield sodium salt of 5-ethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol -5-yl)-2-pyrrolyl]- benzyl]-7-methyl-3H-imidazo[4,5-b]: pyridine (107.9mg) as off-white powder.

NMR(DMSO-d_6, δ):

0.96(3H,t, J=7.5Hz), 1.22(3H,t, J=7.5Hz),
1.31(3H,t, J=7.5Hz), 2.24(3H,s), 2.48(3H,s),
2.80(2H,q, J=7.5Hz), 3.68(2H,q, J=7.5Hz),
4.33(2H,q, J=7.5Hz), 5.40(2H,s),

6.10(1H,s), 6.48(1H,s), 7.15(2H,d, J=8.5Hz),
7.32(2H,d, J=8.5Hz).

Example 34

Sodium (920mg) and distilled trifluoroethanol (8ml) were combined. The mixture was stirred to give a clear solution and then was added 5-bromo-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl] benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (202mg) to the solution. The mixture was refluxed for 72 hours under nitrogen. After being cooled to room temperature, dichloromethane and 1N hydrochloric acid until pH4 to the mixture. The separated organic layer was dried over magesium sulfate and evaporated in vacuo. The residue was crystallized from 99% acetonitrile, and the solvent was evaporated in vacuo. To the residue was added 99% acetonitrile (2ml).
The solid was collected by filtration, and dried in air to give 2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-5-(2,2,2-trifluoroethoxy)-3H-imidazo[4,5-b]pyridine (125mg) as pale brown powder.

mp. 210-220 ℃
NMR(DMSO-d_6, δ):
1.00(3H,t, J=7.5Hz), 1.21(3H,t, J=7.5Hz),
2.28(3H,s), 2.49(3H,s), 2.83(2H,q, J=7.5Hz),
3.70(2H,q, J=7.5Hz), 5.03(2H,q, J=9Hz),
5.50(2H,s), 6.34(1H,s), 6.67(1H,s),
7.30(4H,s).

Example 35

The following compound was obtained according to a similar manner to that of Example 33.

Sodium salt of 2-ethyl-3-[4-[1-ethyl-5-methyl-

3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-5-(2,2,2-trifluoroethoxy)-3H-imidazo[4,5-b]pyridine.

NMR(DMSO-d_6, δ):

0.97(3H,t, J=7.5Hz), 1.23(3H,t, J=7.5Hz),
2.25(3H,s), 2.53(3H,s), 2.82(2H,q, J=7.5Hz),
3.67(2H,br.q, J=7.5Hz), 5.05(2H,q, J=10Hz),
6.10(1H,s), 6.66(1H,s), 7.16(2H,d, J=9Hz),
7.32(2H,d, J=9Hz)

Example 36

5-Carboxy-2-ethyl-3-[4-(1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine (170mg), 2-propanol (1.7ml) and conc. sulfuric acid (170ml) were combined under nitrogen atomosphere. The reaction mixture was stirred at 87 ℃ under reflux for 2 hours.
After cooled to room temperature was dissolved in 2-propanol, and neutralized with 1N sodium hydroxide. The mixture was concentrated in vacuo. The residue was purified by preparative thin layer chromatography to give 2-ethyl-3-[4-1-ethyl-5-methyl-3-1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-isopropoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (67.3mg) as white solid.
mp. 124-130 ℃

NMR(DMSO-d_6, δ):

1.02(3H,t, J=7.5Hz), 1.26(3H,t, J=7.5Hz),
1.35(6H,d, J=6.5Hz), 2.29(3H,s), 2.63(3H,s),
2.90(2H,q, J=7.5Hz), 3.72(2H,q, J=7.5Hz),
5.17(1H,q, J=6.5Hz), 5.61(2H,s),
6.33(1H,s), 7.21(2H,d, J=8.5Hz),
7.31(2H,d, J=8.5Hz), 7.86(1H,s).

Example 37

2-Ethyl-3-[4-1-ethyl-5-methyl-3-(-1H-tetrazol-5-yl) -2-pyrrolyl] benzyl] -5- isopropoxycarbonyl

-7-methyl-3H-imidazo[4,5-b]pyridine(63.3mg), 1N sodium hydroxide (123.5ml) and water (1ml) were combined, and dissolved. The mixture was filtered through a millipore filter and the filtrate was lyophilized to yield sodium salt of
2-ethyl-3-[4-1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-5-isopropoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine(63.7mg) as off-white powder.

NMR(DMSO-d_6, δ):
0.97(3H,t, J=7.5Hz), 1.26(3H,t, J=7.5Hz),
1.37(6H,d, J=6.0Hz), 2.23(3H,s), 2.63(3H,s),
2.90(2H,q, J=7.5Hz), 3.69(2H,q, J=7.5Hz),
5.18(1H,q, J=6.0Hz), 5.57(2H,s), 6.11(1H,s),
7.13(2H,d, J=9.0Hz), 7.34(2H,d, J=9.0Hz),
7.85(1H,s).

Example 38

2-Ethyl-3-[4-1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)pyrrolyl]benzyl]-5-isopropoxycarbonyl-7-methyl-3H-imidazo[4,5-b]pyridine (170mg) was dissolved in 3.5ml of tetrahydrofuran under nitrogen atmosphere, and triethylamine (132 μ l) and ethyl chloroformate (45.6 μ l) were added to the solution at 0 ℃ .
The reaction mixture was stirred at room temperature for one hour, and then 50% aqueous trimethylamine (3ml) was added to the mixture. The reaction mixture was stirred at room temperature for one hour. Water was added to the mixture, and extracted with chloroform twice. The combined organic layers were dried over magnesium sulfate and evaporated. The residue was purified by preparative thin layer chromatography on silica gel (developed by methanol/dichloromethane = 1/10) to give

N,N-dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl] benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide (53.7mg) as white solid.

mp. 199~203 ℃

NMR($CDCl_3$, δ):

1.07(3H,t, J=7.5Hz), 1.29(3H,t, J=7.5Hz),
2.31(3H,s), 2.72(3H,s), 2.82(2H,q, J=7.5Hz),
3.00(3H,s), 3.11(3H,s), 3.72(2H,q, J=7.5Hz),
5.46(2H,s), 6.51(1H,s), 6.94~7.08 (9H,m),
7.15~7.34(10H,m), 7.43(1H,s).

Example 39

N,N- Dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1-triphenylmethyl-1H-tetrazol-5-yl)-2-pyrrolyl]-benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide(50mg), ethanol (1ml) and 4N hydrochloric acid-dioxane (0. 2ml) were combined, and stirred at room temperature for one hour under nitrogen atmosphere.
The mixture was concentrated in vacuo, and the residue was dissolved in ethanol. The solution was neutralized with 1N-sodium hydroxide, and concentrated in vacuo.
The residue was purified by preparative thin layer chromatography on silica gel (developed by methanol/dichloromethane = 1/9).
The amorphous was solidified with diisopropyl ether to give
N,N-dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide (22.4mg) as off-white solid.

mp. 126-134 ℃

NMR(CD_3OD-$CDCl_3$, δ):

1.11(3H,t, J=7.5Hz), 1.39(3H,t, J=7.5Hz),

2.33(3H,s), 2.71(3H,s), 2.97(2H,q, J=7.5Hz),
3.03(3H,s), 3.16(3H,s), 3.76(2H,q, J=7.5Hz),
5.56(2H,s), 6.40(1H,s), 7.19(2H,d, J=8.5Hz),
7.28(2H,d, J=8.5Hz), 7.35(1H,s).

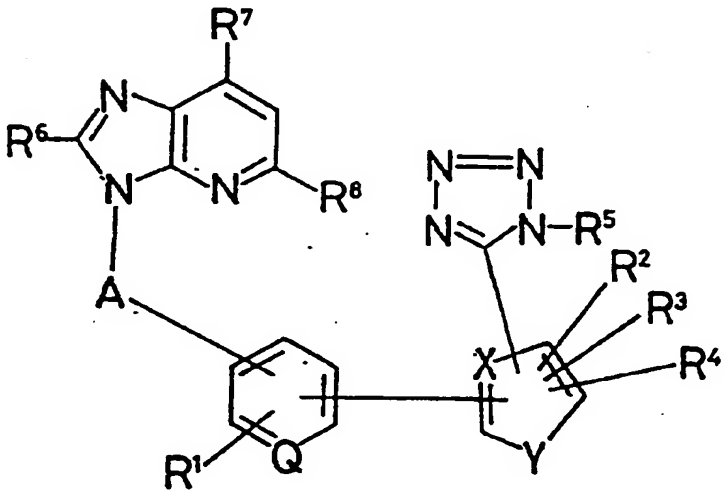
Example 40

N,N-Dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide(20.3mg), 1N-sodium hydroxide (40.8 μl) and water (0.5ml) were combined, and dissolved. The mixture was filtered through a millipore filter, and the filtrate was lyophilized to yield sodium salt of N,N-dimethyl-2-ethyl-3-[4-[1-ethyl-5-methyl-3-(1H-tetrazol-5-yl)-2-pyrrolyl]benzyl]-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide(21.2mg) as white powder.

NMR(DMSO-d_6, δ):
0.96(3H,t,J=7.5Hz), 1.29(3H,t,J=7.5Hz),
2.22(3H,s), 2.60(3H,s), 2.90(3H,s),
2.92(2H,q,J=7.5Hz), 3.00(3H,s),
3.67(2H,q,J=7.5Hz), 5.52(2H,s), 6.10(1H,s),
7.10(2H,d,J=8.5Hz), 7.30(1H,s),
7.32(2H,d,J=8.5Hz).

CLAIMS

1. A compound of the formula :



wherein R^1 is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, amino or acylamino,

R^2, R^3 and R^4 are each hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkylthio, mono or di or trihalo (lower) alkyl, oxo (lower) alkyl, hydroxy (lower) alkyl or optionally esterified carboxy ; or

R^2 and R^3 are linked together to form 1,3 — butadienylene,

R^5 is hydrogen or imino — protective group,

R^6 is lower alkyl,

R^7 is lower alkyl,

R^8 is optionally esterified or amidated carboxy, halogen, cyano, hydroxy (lower) alkyl, or lower alkoxy which may have halogen,

A is lower alkylene,

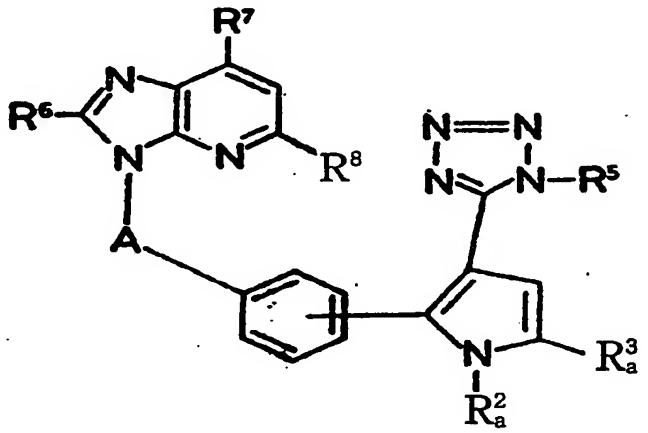
Q is CH or N,

X is N or CH and

Y is NH, O or S,

and pharmaceutically acceptable salt thereof.

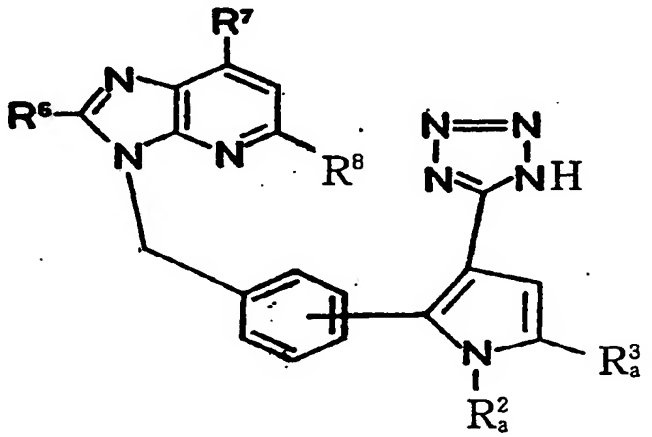
2. A compound of claim 1, which is represented by the formula :



wherein R^5, R^6, R^7, R^8 and A are each as defined in claim 1, and R_a^2 and R_a^3 are each lower alkyl.

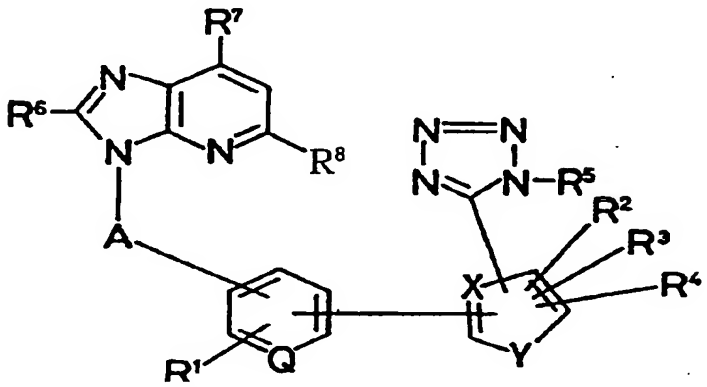
3. A compound of claim 2, wherein R^8 is carboxy, lower alkoxycarbonyl, carbamoyl, mono — or di (lower) alkylcarbamoyl, N — hydroxy — N — (lower) alkylcarbamoyl, lower alkylsulfonylcarbamoyl, 1 — carboxyphenethylcarbamoyl, 1 — (lower alkoxycarbonyl) phenethylcarbamoyl, halogen, cyano, hydroxy (lower) alkyl or lower alkoxy which may have halogen.

4. A compound of claim 3, which is represented by the formula :



wherein R^6, R^7, R^8, R^2_a and R^3_a are each as defined in claim 3.

5. **A process for preparing a compound of the formula :**



wherein R^1 is hydrogen, halogen, nitro, lower alkyl, lower alkoxy, amino or acylamino,

R^2, R^3 and R^4 are each hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkylthio, mono or di or trihalo (lower) alkyl, oxo (lower) alkyl, hydroxy (lower) alkyl or optionally esterified carboxy ; or

R^2 and R^3 are linked together to form 1,3 — butadienylene,

R^5 is hydrogen or imino — protective group,

R^6 is lower alkyl,

R^7 is lower alkyl,

R^8 is optionally esterified or amidated carboxy, halogen, cyano, hydroxy (lower) alkyl, or lower alkoxy which may have halogen,

A is lower alkylene,

Q is CH or N,

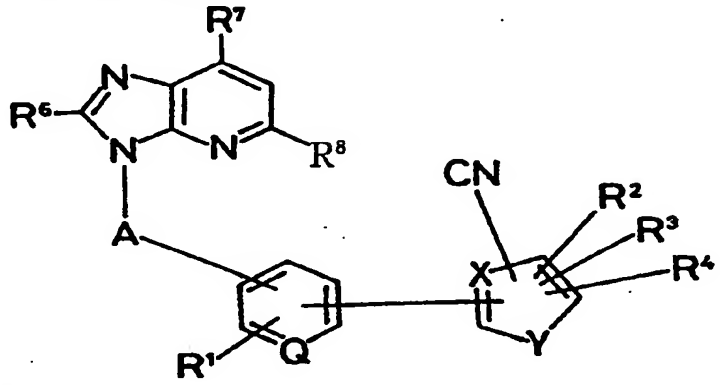
X is N or CH and

Y is NH, O or S,

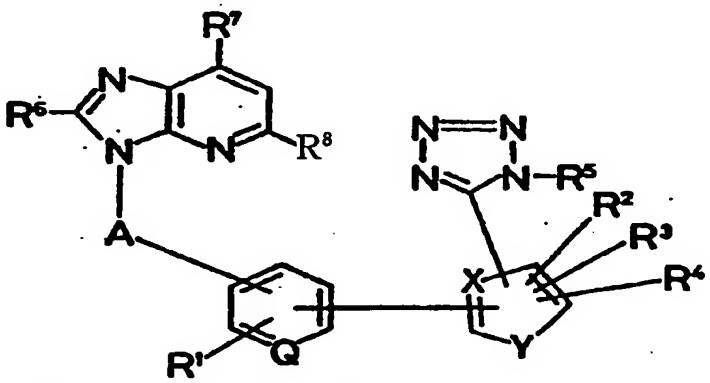
or a salt thereof,

which comprises

a) subjecting a compound of the formula :

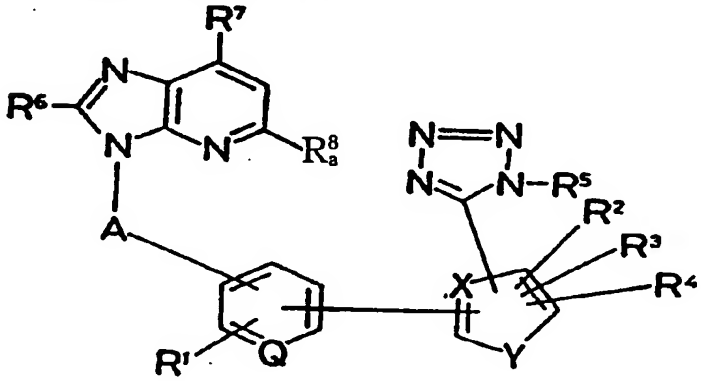


wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, Q, X and Y are each as defined above, to formation reaction of a tetrazole group, to give a compound of the formula :

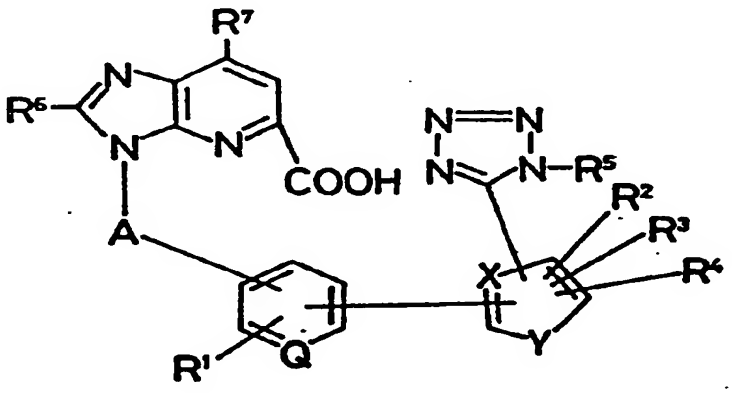


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, Q, X and Y are each as defined above, or a salt thereof, or

b) subjecting a compound of the formula :

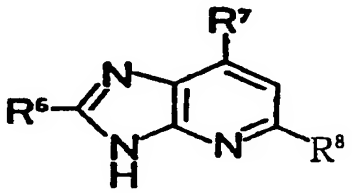


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y
are each as defined above,
and
R^8_a is esterified carboxy,
or a salt thereof, to elimination reaction of the ester moiety, to give a compound of the formula :

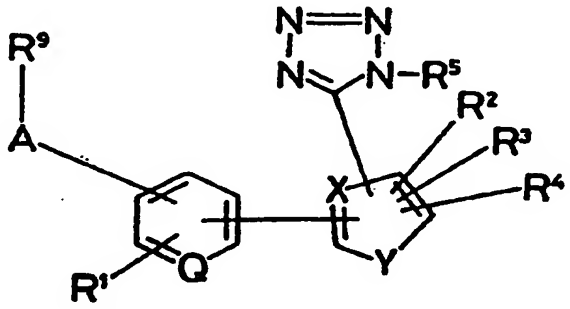


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y
are each as defined above,
or a salt thereof or

c) reacting a compound of the formula :



wherein R^6, R^7, and R^8 are each as defined above,
or a salt thereof,
with a compound of the formula :

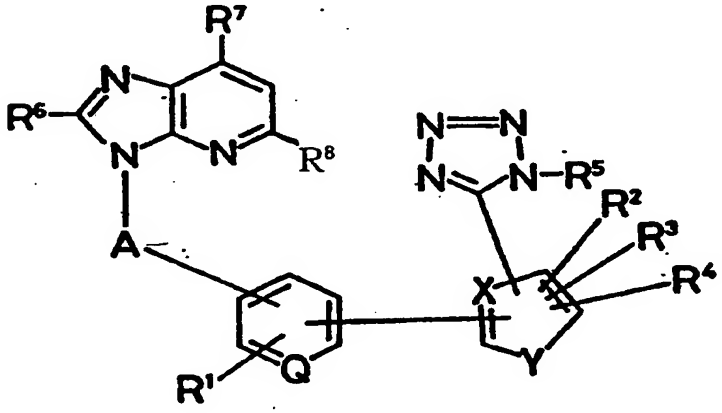


wherein R^1, R^2, R^3, R^4, R^5, A, Q, X and Y are each as defined above, and

R^9 is acid residue,

or a salt thereof,

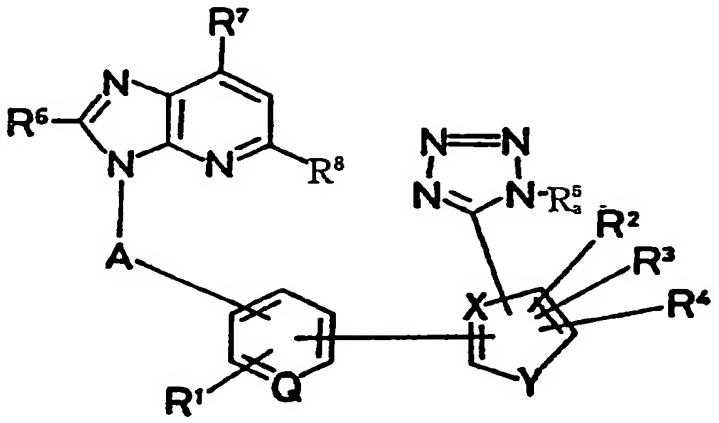
to give a compound of the formula :



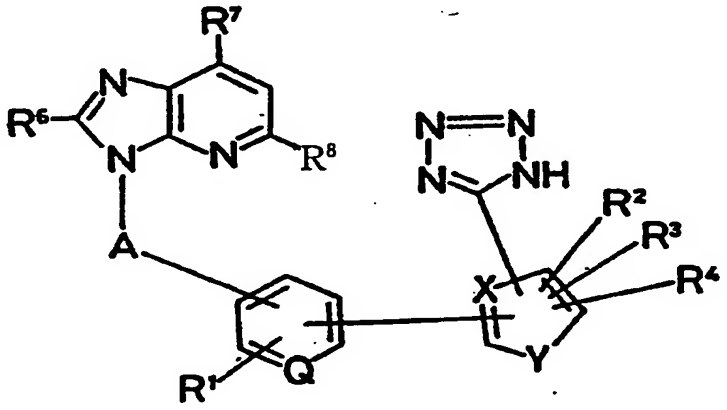
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, Q, X and Y are each as defined above,

or a salt thereof or

d) subjecting a compound of the formula :

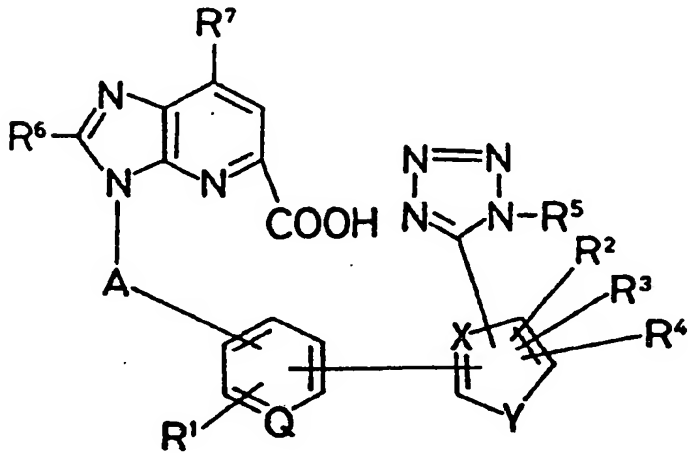


wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, Q, X and Y are each as defined above, and R^5_a is imino-protective group, or a salt thereof, to removal of the imino-protective group, to give a compound of the formula :



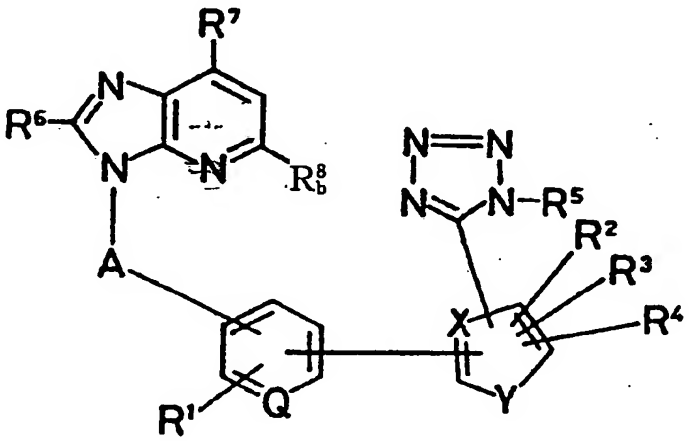
wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, Q, X and Y are each as defined above, or a salt therof, or

e) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y

are each as defined above, or its reactive derivative at the carboxy group, or a salt thereof, to amidation, to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y

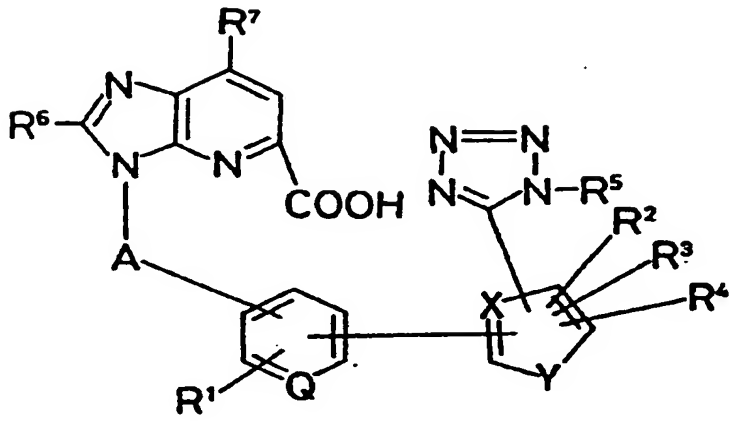
are each as defined above,

and

R^8_b is amidated carboxy,

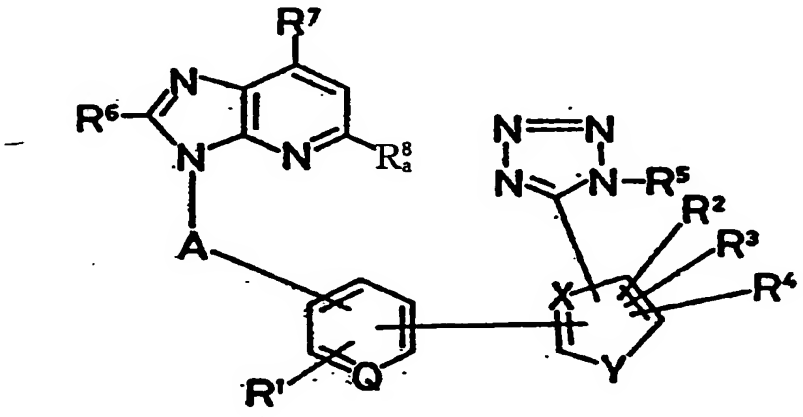
or a salt thereof or

f) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above,

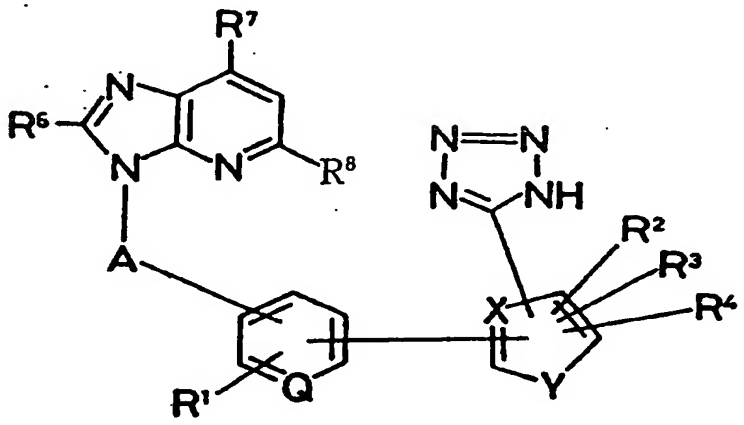
or its reactive derivative at the carboxy group, or a salt thereof, to esterification, to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8_a, A, Q, X and Y are each as defined above, and

or a salt thereof or

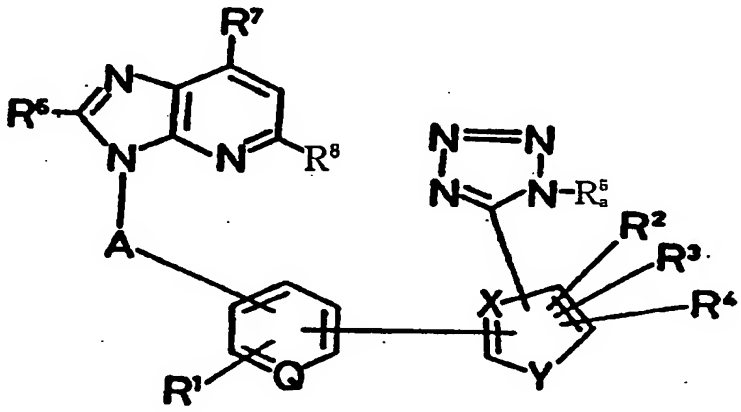
g) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, Q, X and Y

are each as defined above,

or a salt thereof, to introduction of the imino-protective group, to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, Q, X and Y

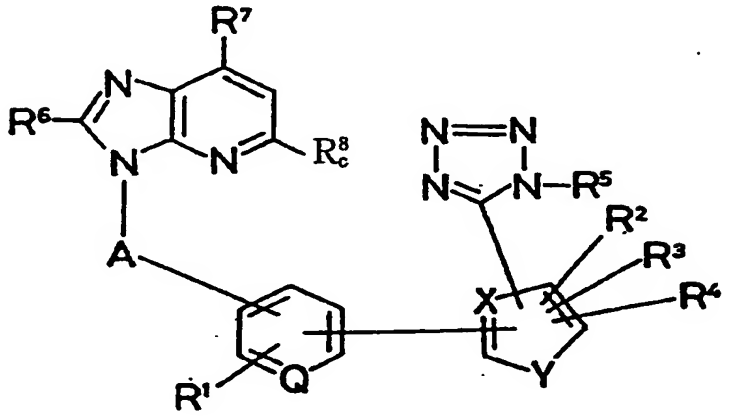
are each as defined above,

and

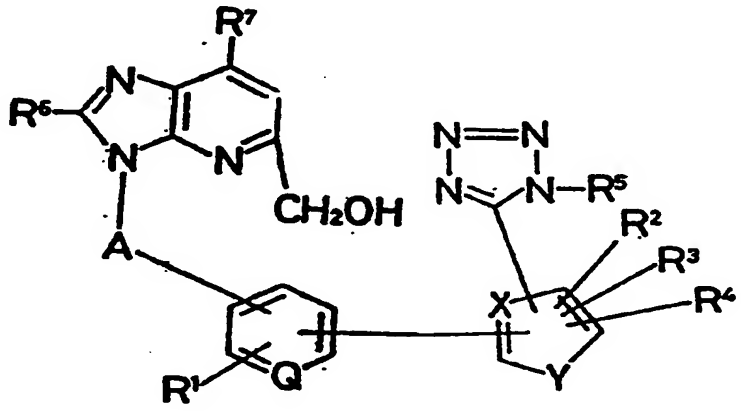
R^5_a **is imino-protective group,**

or a salt therof, or

h) subjecting a compound of the formula :



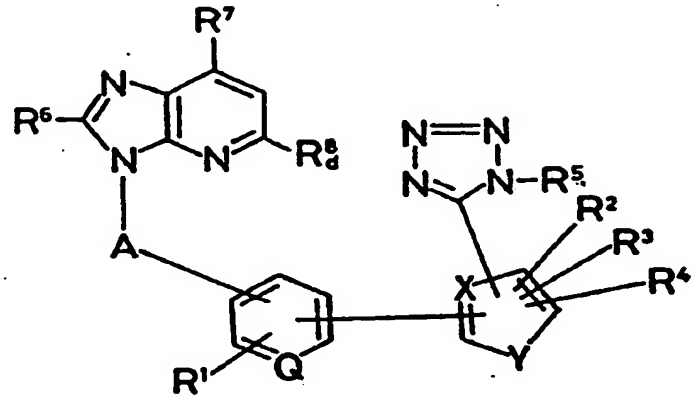
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above, R^8_c is optionally esterified carboxy or a salt thereof, to reduction to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above, and

or a salt therof, or

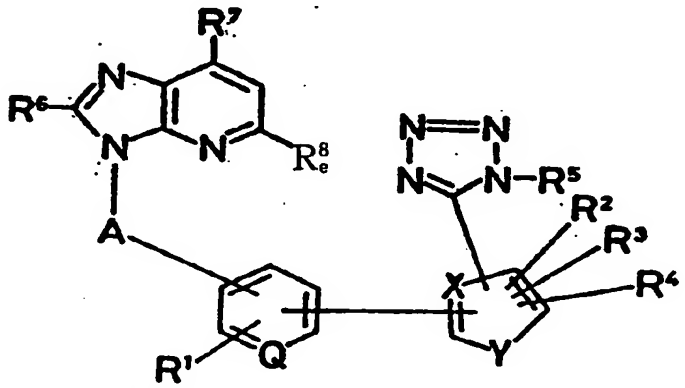
i) reacting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above, and R^8_d is halogen, or a salt thereof, with a compound of the formula :

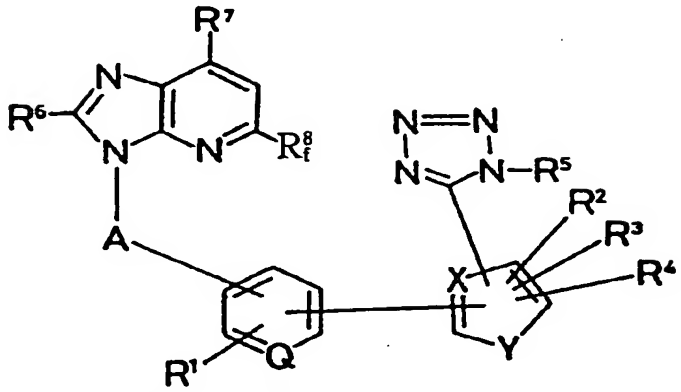
$$M - R^8_e$$

wherein R^8_e is lower alkoxy which may have halogen, and M is alkali metal, to give a compound of the formula :

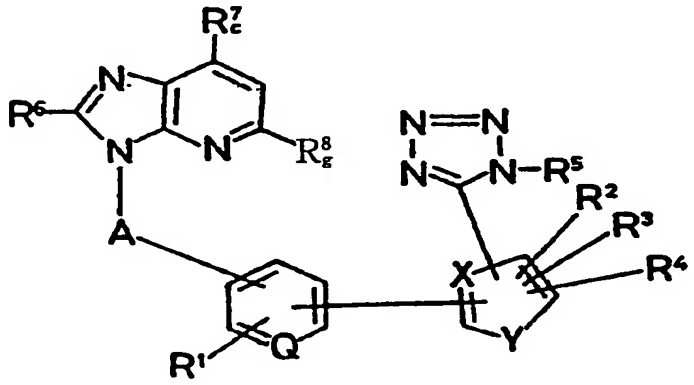


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8_e, A, Q, X and Y are each as defined above, or a salt thereof, or

j) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above, and R^8_f is amidated carboxy, having esterified carboxy, or a salt thereof, to elimination reaction of the ester moiety, to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, Q, X and Y are each as defined above, and R^8_g is amidated carboxy, or a salt thereof.

6. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with apharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A method for treating or preventing angiotensin II mediated diseases, which comprises administering a compound of claim 1 or pharmaceutically acceptable salt thereof to human being or animals.

8. A method for treating or preventing hypertension or heart failure, which comprises administering a compound of claim 1 or pharmaceutically acceptable salt thereof to human being or animals.

9. A compound of claim 1 or pharmaceutically acceptable salt thereof for use as a medicament.

10. A compound of claim 1 or pharmaceutically acceptable salt thereof for use as an angiotensin II antagonist.

11. Use of a compound of claim 1 for manufacturing a medicament for treating or preventing angiotensin II mediated diseases.

12. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable substantially non-toxic carrier or excipient.